

NOVEL POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**FIELD OF THE INVENTION**

The present invention relates generally to the identification and isolation of novel DNA and to the recombinant production of novel polypeptides encoded by that DNA.

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BACKGROUND OF THE INVENTION

Extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

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Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.* 93:7108-7113 (1996); U.S. Patent No. 5,536,637].

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Membrane-bound proteins and receptors can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

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35 Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents

to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Efforts are being undertaken by both industry and academia to identify new, native receptor proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins.

We herein describe the identification and characterization of novel secreted and transmembrane polypeptides
5 and novel nucleic acids encoding those polypeptides.

1. PRO213

Human growth arrest-specific gene 6 (*gas6*) encodes a protein that is expressed in a variety of different tissues and which has been reported to be highly expressed during periods of serum starvation and negatively
10 regulated during growth induction. See Manfioletti et al., *Mol. Cell. Biol.* 13(8):4976-4985 (1993) and Stitt et al., *Cell* 80:661-670 (1995). Manfioletti et al. (1993), *supra*, have suggested that the *gas6* protein is member of the vitamin K-dependent family of proteins, wherein the members of the latter family of proteins (which include, for example, Protein S, Protein C and Factor X) all play regulatory roles in the blood coagulation pathway. Thus, it has been suggested that *gas6* may play a role in the regulation of a protease cascade relevant in growth regulation or in
15 the blood coagulation cascade.

Given the physiological importance of the *gas6* protein, efforts are currently being undertaken by both industry and academia to identify new, native proteins which are homologous to *gas6*. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins, specifically those having homology to *gas6*. Examples of such
20 screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.* 93:7108-7113 (1996); U.S. Patent No. 5,536,637]. We herein describe the identification of a novel polypeptide which has homology to the *gas6* polypeptide.

2. PRO274

The 7-transmembrane ("7TM") proteins or receptors, also referred to in the literature as G-protein coupled receptors, are specialized proteins designed for recognition of ligands and the subsequent signal transduction of information contained within those ligands to the machinery of the cell. The primary purpose of cell surface receptors is to discriminate appropriate ligands from the various extracellular stimuli which each cell encounters, then to activate an effector system that produces an intracellular signal, thereby controlling cellular processes. [Dohman,
25 H., *Ann. Rev. Biochem.*, 60:653 (1991)]. The ability of 7TM receptors to bind ligand to a recognition domain and allosterically transmit the information to an intracellular domain is a specialized feature of 7TM proteins [Kenakin, T., *Pharmacol. Rev.*, 48:413 (1996)]. The gene family which encodes the 7TM receptors or G-protein linked receptors encode receptors which recognize a large number of ligands, including but not limited to, CSa, interleukin 8 and related chemokines. Research in this area suggests that distinct signals at the cell surface feed into common
30 pathways of cell activation. [Gerard, C. and Gerard, N., *Curr. Op. Immunol.*, 6:140 (1994), Gerard, C. and Gerard, N., *Ann. Rev. Immunol.*, 12:775 (1994)]. The superfamily of 7TM or G-protein coupled receptors contains several hundred members able to recognize various messages such as photons, ions and amino acids among others [Schwartz, T.W., et al., H., *Trends in Pharmacol. Sci.*, 17(6):213 (1996)].
35 [Dohman, H., *Ann. Rev. Biochem.*, 60:653 (1991)]. [Schwartz, T.W., et al., H., *Eur. J. Pharm. Sci.*, 2:85 (1994)].

We describe herein the identification of a novel polypeptide (designated herein as PRO274) which has homology to the 7 transmembrane segment receptor proteins and the Fn54 protein.

3. **PRO300**

The Diff 33 protein is over-expressed in mouse testicular tumors. At present its role is unclear, however, 5 it may play a role in cancer. Given the medical importance of understanding the physiology of cancer, efforts are currently being undertaken to identify new, native proteins which are involved in cancer. We describe herein the identification of a novel polypeptide which has homology to Diff 33, designated herein as PRO300.

4. **PRO284**

10 Efforts are currently being undertaken to identify and characterize novel transmembrane proteins. We herein describe the identification and characterization of a novel transmembrane polypeptide, designated herein as PRO284.

5. **PRO296**

15 Cancerous cells often express numerous proteins that are not expressed in the corresponding normal cell type or are expressed at different levels than in the corresponding normal cell type. Many of these proteins are involved in inducing the transformation from a normal cell to a cancerous cell or in maintaining the cancer phenotype. As such, there is significant interest in identifying and characterizing proteins that are expressed in cancerous cells. We herein describe the identification and characterization of a novel polypeptide having homology to the sarcoma- 20 amplified protein SAS, designated herein as PRO296.

6. **PRO329**

Immunoglobulin molecules play roles in many important mammalian physiological processes. The structure 25 of immunoglobulin molecules has been extensively studied and it has been well documented that intact immunoglobulins possess distinct domains, one of which is the constant domain or F_c region of the immunoglobulin molecule. The F_c domain of an immunoglobulin, while not being directly involved in antigen recognition and binding, does mediate the ability of the immunoglobulin molecule, either uncomplexed or complexed with its respective antigen, to bind to F_c receptors either circulating in the serum or on the surface of cells. The ability of an F_c domain of an immunoglobulin to bind to an F_c receptor molecule results in a variety of important activities, including for 30 example, in mounting an immune response against unwanted foreign particles. As such, there is substantial interest in identifying novel F_c receptor proteins and subunits thereof. We herein describe the identification and characterization of a novel polypeptide having homology to a high affinity immunoglobulin F_c receptor protein, designated herein as PRO329.

35 7. **PRO362**

Colorectal carcinoma is a malignant neoplastic disease which has a high incidence in the Western world, particularly in the United States. Tumors of this type often metastasize through lymphatic and vascular channels and result in the death of some 62,000 persons in the United States annually.

Monoclonal antibody A33 (mAbA33) is a murine immunoglobulin that has undergone extensive preclinical analysis and localization studies in patients inflicted with colorectal carcinoma (Welt et al., *J. Clin. Oncol.* 8:1894-1906 (1990) and Welt et al., *J. Clin. Oncol.* 12:1561-1571 (1994)). mAbA33 has been shown to bind to an antigen found in and on the surface of normal colon cells and colon cancer cells. In carcinomas originating from the colonic mucosa, the A33 antigen is expressed homogeneously in more than 95% of the cases. The A33 antigen, however, 5 has not been detecting in a wide range of other normal tissues, i.e., its expression appears to be rather organ specific. Therefore, the A33 antigen appears to play an important role in the induction of colorectal cancer.

Given the obvious importance of the A33 antigen in tumor cell formation and/or proliferation, there is substantial interest in identifying homologs of the A33 antigen. In this regard, we herein describe the identification and characterization of a novel polypeptide having homology to the A33 antigen protein, designated herein as 10 PRO362.

8. PRO363

The cell surface protein HCAR is a membrane-bound protein that acts as a receptor for subgroup C of the adenoviruses and subgroup B of the coxsackieviruses. Thus, HCAR may provide a means for mediating viral 15 infection of cells in that the presence of the HCAR receptor on the cellular surface provides a binding site for viral particles, thereby facilitating viral infection.

In light of the physiological importance of membrane-bound proteins and specifically those which serve a cell surface receptor for viruses, efforts are currently being undertaken by both industry and academia to identify new, native membrane-bound receptor proteins. Many of these efforts are focused on the screening of mammalian 20 recombinant DNA libraries to identify the coding sequences for novel receptor proteins. We herein describe a novel membrane-bound polypeptide having homology to the cell surface protein HCAR and to various tumor antigens including A33 and carcinoembryonic antigen, designated herein as PRO363, wherein this polypeptide may be a novel cell surface virus receptor or tumor antigen.

25 9. PRO868

Control of cell numbers in mammals is believed to be determined, in part, by a balance between cell proliferation and cell death. One form of cell death, sometimes referred to as necrotic cell death, is typically characterized as a pathologic form of cell death resulting from some trauma or cellular injury. In contrast, there is another, "physiologic" form of cell death which usually proceeds in an orderly or controlled manner. This orderly 30 or controlled form of cell death is often referred to as "apoptosis" [see, e.g., Barr et al., *Bio/Technology*, 12:487-493 (1994); Steller et al., *Science*, 267:1445-1449 (1995)]. Apoptotic cell death naturally occurs in many physiological processes, including embryonic development and clonal selection in the immune system [Itoh et al., *Cell*, 66:233-243 (1991)]. Decreased levels of apoptotic cell death have been associated with a variety of pathological conditions, including cancer, lupus, and herpes virus infection [Thompson, *Science*, 267:1456-1462 (1995)]. Increased levels 35 of apoptotic cell death may be associated with a variety of other pathological conditions, including AIDS, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, retinitis pigmentosa, cerebellar degeneration, aplastic anemia, myocardial infarction, stroke, reperfusion injury, and toxin-induced liver disease [see, Thompson, *supra*].

Apoptotic cell death is typically accompanied by one or more characteristic morphological and biochemical changes in cells, such as condensation of cytoplasm, loss of plasma membrane microvilli, segmentation of the nucleus, degradation of chromosomal DNA or loss of mitochondrial function. A variety of extrinsic and intrinsic signals are believed to trigger or induce such morphological and biochemical cellular changes [Raff, *Nature*, **356**:397-400 (1992); Steller, *supra*; Sachs et al., *Blood*, **82**:15 (1993)]. For instance, they can be triggered by hormonal stimuli, such as glucocorticoid hormones for immature thymocytes, as well as withdrawal of certain growth factors [Watanabe-Fukunaga et al., *Nature*, **356**:314-317 (1992)]. Also, some identified oncogenes such as *myc*, *rel*, and *EIA*, and tumor suppressors, like *p53*, have been reported to have a role in inducing apoptosis. Certain chemotherapy drugs and some forms of radiation have likewise been observed to have apoptosis-inducing activity [Thompson, *supra*].

Various molecules, such as tumor necrosis factor- α ("TNF- α "), tumor necrosis factor- β ("TNF- β " or "lymphotoxin- α "), lymphotoxin- β ("LT- β "), CD30 ligand, CD27 ligand, CD40 ligand, OX-40 ligand, 4-1BB ligand, Apo-1 ligand (also referred to as Fas ligand or CD95 ligand), and Apo-2 ligand (also referred to as TRAIL) have been identified as members of the tumor necrosis factor ("TNF") family of cytokines [See, e.g., Gruss and Dower, *Blood*, **85**:3378-3404 (1995); Pitti et al., *J. Biol. Chem.*, **271**:12687-12690 (1996); Wiley et al., *Immunity*, **3**:673-682 (1995); Browning et al., *Cell*, **72**:847-856 (1993); Armitage et al. *Nature*, **357**:80-82 (1992), WO 97/01633 published January 16, 1997; WO 97/25428 published July 17, 1997]. Among these molecules, TNF- α , TNF- β , CD30 ligand, 4-1BB ligand, Apo-1 ligand, and Apo-2 ligand (TRAIL) have been reported to be involved in apoptotic cell death. Both TNF- α and TNF- β have been reported to induce apoptotic death in susceptible tumor cells [Schmid et al., *Proc. Natl. Acad. Sci.*, **83**:1881 (1986); Dealy et al., *Eur. J. Immunol.*, **17**:689 (1987)]. Zheng et al. have reported that TNF- α is involved in post-stimulation apoptosis of CD8-positive T cells [Zheng et al., *Nature*, **377**:348-351 (1995)]. Other investigators have reported that CD30 ligand may be involved in deletion of self-reactive T cells in the thymus [Amakawa et al., Cold Spring Harbor Laboratory Symposium on Programmed Cell Death, Abstr. No. 10, (1995)].

Mutations in the mouse Fas/Apo-1 receptor or ligand genes (called *lpr* and *gld*, respectively) have been associated with some autoimmune disorders, indicating that Apo-1 ligand may play a role in regulating the clonal deletion of self-reactive lymphocytes in the periphery [Krammer et al., *Curr. Op. Immunol.*, **6**:279-289 (1994); Nagata et al., *Science*, **267**:1449-1456 (1995)]. Apo-1 ligand is also reported to induce post-stimulation apoptosis in CD4-positive T lymphocytes and in B lymphocytes, and may be involved in the elimination of activated lymphocytes when their function is no longer needed [Krammer et al., *supra*; Nagata et al., *supra*]. Agonist mouse monoclonal antibodies specifically binding to the Apo-1 receptor have been reported to exhibit cell killing activity that is comparable to or similar to that of TNF- α [Yonehara et al., *J. Exp. Med.*, **169**:1747-1756 (1989)].

Induction of various cellular responses mediated by such TNF family cytokines is believed to be initiated by their binding to specific cell receptors. Two distinct TNF receptors of approximately 55-kDa (TNFR1) and 75-kDa (TNFR2) have been identified [Hohman et al., *J. Biol. Chem.*, **264**:14927-14934 (1989); Brockhaus et al., *Proc. Natl. Acad. Sci.*, **87**:3127-3131 (1990); EP 417,563, published March 20, 1991] and human and mouse cDNAs corresponding to both receptor types have been isolated and characterized [Loetscher et al., *Cell*, **61**:351 (1990); Schall et al., *Cell*, **61**:361 (1990); Smith et al., *Science*, **248**:1019-1023 (1990); Lewis et al., *Proc. Natl. Acad. Sci.*, **88**:2830-2834 (1991); Goodwin et al., *Mol. Cell. Biol.*, **11**:3020-3026 (1991)]. Extensive polymorphisms have been associated with both TNF receptor genes [see, e.g., Takao et al., *Immunogenetics*, **37**:199-203 (1993)]. Both TNFRs share the typical structure of cell surface receptors including extracellular, transmembrane and intracellular regions.

The extracellular portions of both receptors are found naturally also as soluble TNF-binding proteins [Nophar, Y. et al., *EMBO J.*, **9**:3269 (1990); and Kohno, T. et al., *Proc. Natl. Acad. Sci. U.S.A.*, **87**:8331 (1990)]. More recently, the cloning of recombinant soluble TNF receptors was reported by Hale et al. [*J. Cell. Biochem. Supplement* **15F**, 1991, p. 113 (P424)].

5 The extracellular portion of type 1 and type 2 TNFRs (TNFR1 and TNFR2) contains a repetitive amino acid sequence pattern of four cysteine-rich domains (CRDs) designated 1 through 4, starting from the NH₂-terminus. Each CRD is about 40 amino acids long and contains 4 to 6 cysteine residues at positions which are well conserved [Schall et al., *supra*; Loetscher et al., *supra*; Smith et al., *supra*; Nophar et al., *supra*; Kohno et al., *supra*]. In TNFR1, the approximate boundaries of the four CRDs are as follows: CRD1- amino acids 14 to about 53; CRD2- amino acids from about 54 to about 97; CRD3- amino acids from about 98 to about 138; CRD4- amino acids from about 139 to 10 about 167. In TNFR2, CRD1 includes amino acids 17 to about 54; CRD2- amino acids from about 55 to about 97; CRD3- amino acids from about 98 to about 140; and CRD4- amino acids from about 141 to about 179 [Banner et al., *Cell*, **73**:431-435 (1993)]. The potential role of the CRDs in ligand binding is also described by Banner et al., *supra*.

A similar repetitive pattern of CRDs exists in several other cell-surface proteins, including the p75 nerve growth factor receptor (NGFR) [Johnson et al., *Cell*, **47**:545 (1986); Radeke et al., *Nature*, **325**:593 (1987)], the B 15 cell antigen CD40 [Stamenkovic et al., *EMBO J.*, **8**:1403 (1989)], the T cell antigen OX40 [Mallet et al., *EMBO J.*, **9**:1063 (1990)] and the Fas antigen [Yonehara et al., *supra* and Itoh et al., *Cell*, **66**:233-243 (1991)]. CRDs are also found in the soluble TNFR (sTNFR)-like T2 proteins of the Shope and myxoma poxviruses [Upton et al., *Virology*, **160**:20-29 (1987); Smith et al., *Biochem. Biophys. Res. Commun.*, **176**:335 (1991); Upton et al., *Virology*, **184**:370 (1991)]. Optimal alignment of these sequences indicates that the positions of the cysteine residues are well conserved. 20 These receptors are sometimes collectively referred to as members of the TNF/NGF receptor superfamily. Recent studies on p75NGFR showed that the deletion of CRD1 [Welcher, A.A. et al., *Proc. Natl. Acad. Sci. USA*, **88**:159-163 (1991)] or a 5-amino acid insertion in this domain [Yan, H. and Chao, M.V., *J. Biol. Chem.*, **266**:12099-12104 (1991)] had little or no effect on NGF binding [Yan, H. and Chao, M.V., *supra*]. p75 NGFR contains a proline-rich stretch of about 60 amino acids, between its CRD4 and transmembrane region, which is not involved in NGF binding. 25 [Peetre, C. et al., *Eur. J. Hematol.*, **41**:414-419 (1988); Seckinger, P. et al., *J. Biol. Chem.*, **264**:11966-11973 (1989); Yan, H. and Chao, M.V., *supra*]. A similar proline-rich region is found in TNFR2 but not in TNFR1.

The TNF family ligands identified to date, with the exception of lymphotoxin- α , are type II transmembrane proteins, whose C-terminus is extracellular. In contrast, most receptors in the TNF receptor (TNFR) family identified to date are type I transmembrane proteins. In both the TNF ligand and receptor families, however, homology 30 identified between family members has been found mainly in the extracellular domain ("ECD"). Several of the TNF family cytokines, including TNF- α , Apo-1 ligand and CD40 ligand, are cleaved proteolytically at the cell surface; the resulting protein in each case typically forms a homotrimeric molecule that functions as a soluble cytokine. TNF receptor family proteins are also usually cleaved proteolytically to release soluble receptor ECDs that can function as inhibitors of the cognate cytokines.

35 Recently, other members of the TNFR family have been identified. Such newly identified members of the TNFR family include CAR1, HVEM and osteoprotegerin (OPG) [Brojatsch et al., *Cell*, **87**:845-855 (1996); Montgomery et al., *Cell*, **87**:427-436 (1996); Marsters et al., *J. Biol. Chem.*, **272**:14029-14032 (1997); Simonet et al., *Cell*, **89**:309-319 (1997)]. Unlike other known TNFR-like molecules, Simonet et al., *supra*, report that OPG contains no hydrophobic transmembrane-spanning sequence.

Moreover, a new member of the TNF/NGF receptor family has been identified in mouse, a receptor referred to as "GITR" for "glucocorticoid-induced tumor necrosis factor receptor family-related gene" [Nocentini et al., *Proc. Natl. Acad. Sci. USA* 94:6216-6221 (1997)]. The mouse GITR receptor is a 228 amino acid type I transmembrane protein that is expressed in normal mouse T lymphocytes from thymus, spleen and lymph nodes. Expression of the mouse GITR receptor was induced in T lymphocytes upon activation with anti-CD3 antibodies, Con A or phorbol 5 12-myristate 13-acetate. It was speculated by the authors that the mouse GITR receptor was involved in the regulation of T cell receptor-mediated cell death.

In Marsters et al., *Curr. Biol.*, 6:750 (1996), investigators describe a full length native sequence human polypeptide, called Apo-3, which exhibits similarity to the TNFR family in its extracellular cysteine-rich repeats and resembles TNFR1 and CD95 in that it contains a cytoplasmic death domain sequence [see also Marsters et al., *Curr. Biol.*, 6:1669 (1996)]. Apo-3 has also been referred to by other investigators as DR3, wsl-1 and TRAMP [Chinnaiyan et al., *Science*, 274:990 (1996); Kitson et al., *Nature*, 384:372 (1996); Bodmer et al., *Immunity*, 6:79 (1997)].

Pan et al. have disclosed another TNF receptor family member referred to as "DR4" [Pan et al., *Science*, 276:111-113 (1997)]. The DR4 was reported to contain a cytoplasmic death domain capable of engaging the cell 15 suicide apparatus. Pan et al. disclose that DR4 is believed to be a receptor for the ligand known as Apo-2 ligand or TRAIL.

In Sheridan et al., *Science*, 277:818-821 (1997) and Pan et al., *Science*, 277:815-818 (1997), another molecule believed to be a receptor for the Apo-2 ligand (TRAIL) is described. That molecule is referred to as DR5 (it has also been alternatively referred to as Apo-2). Like DR4, DR5 is reported to contain a cytoplasmic death 20 domain and be capable of signaling apoptosis.

In Sheridan et al., *supra*, a receptor called DcR1 (or alternatively, Apo-2DcR) is disclosed as being a potential decoy receptor for Apo-2 ligand (TRAIL). Sheridan et al. report that DcR1 can inhibit Apo-2 ligand function *in vitro*. See also, Pan et al., *supra*, for disclosure on the decoy receptor referred to as TRID.

For a review of the TNF family of cytokines and their receptors, see Gruss and Dower, *supra*.

As presently understood, the cell death program contains at least three important elements - activators, inhibitors, and effectors; in *C. elegans*, these elements are encoded respectively by three genes, *Ced-4*, *Ced-9* and *Ced-3* [Steller, *Science*, 267:1445 (1995); Chinnaiyan et al., *Science*, 275:1122-1126 (1997); Wang et al., *Cell*, 90:1-20 (1997)]. Two of the TNFR family members, TNFR1 and Fas/Apo1 (CD95), can activate apoptotic cell death [Chinnaiyan and Dixit, *Current Biology*, 6:555-562 (1996); Fraser and Evan, *Cell*, 85:781-784 (1996)]. TNFR1 is 30 also known to mediate activation of the transcription factor, NF- κ B [Tartaglia et al., *Cell*, 74:845-853 (1993); Hsu et al., *Cell*, 84:299-308 (1996)]. In addition to some ECD homology, these two receptors share homology in their intracellular domain (ICD) in an oligomerization interface known as the death domain [Tartaglia et al., *supra*; Nagata, *Cell*, 88:355 (1997)]. Death domains are also found in several metazoan proteins that regulate apoptosis, namely, the *Drosophila* protein, Reaper, and the mammalian proteins referred to as FADD/MORT1, TRADD, and RIP 35 [Cleaveland and Ihle, *Cell*, 81:479-482 (1995)].

Upon ligand binding and receptor clustering, TNFR1 and CD95 are believed to recruit FADD into a death-inducing signalling complex. CD95 purportedly binds FADD directly, while TNFR1 binds FADD indirectly via TRADD [Chinnaiyan et al., *Cell*, 81:505-512 (1995); Boldin et al., *J. Biol. Chem.*, 270:387-391 (1995); Hsu et al., *supra*; Chinnaiyan et al., *J. Biol. Chem.*, 271:4961-4965 (1996)]. It has been reported that FADD serves as an

adaptor protein which recruits the *Ced-3*-related protease, MACH α /FLICE (caspase 8), into the death signalling complex [Boldin et al., *Cell*, **85**:803-815 (1996); Muzio et al., *Cell*, **85**:817-827 (1996)]. MACH α /FLICE appears to be the trigger that sets off a cascade of apoptotic proteases, including the interleukin-1 β converting enzyme (ICE) and CPP32/Yama, which may execute some critical aspects of the cell death programme [Fraser and Evan, *supra*].

5 It was recently disclosed that programmed cell death involves the activity of members of a family of cysteine proteases related to the *C. elegans* cell death gene, *ced-3*, and to the mammalian IL-1-converting enzyme, ICE. The activity of the ICE and CPP32/Yama proteases can be inhibited by the product of the cowpox virus gene, *crmA* [Ray et al., *Cell*, **69**:597-604 (1992); Tewari et al., *Cell*, **81**:801-809 (1995)]. Recent studies show that CrmA can inhibit TNFR1- and CD95-induced cell death [Enari et al., *Nature*, **375**:78-81 (1995); Tewari et al., *J. Biol. Chem.*, **270**:3255-3260 (1995)].

10 As reviewed recently by Tewari et al., TNFR1, TNFR2 and CD40 modulate the expression of proinflammatory and costimulatory cytokines, cytokine receptors, and cell adhesion molecules through activation of the transcription factor, NF- κ B [Tewari et al., *Curr. Op. Genet. Develop.*, **6**:39-44 (1996)]. NF- κ B is the prototype of a family of dimeric transcription factors whose subunits contain conserved Rel regions [Verma et al., *Genes Develop.*, **9**:2723-2735 (1996); Baldwin, *Ann. Rev. Immunol.*, **14**:649-681 (1996)]. In its latent form, NF- κ B is 15 complexed with members of the I κ B inhibitor family; upon inactivation of the I κ B in response to certain stimuli, released NF- κ B translocates to the nucleus where it binds to specific DNA sequences and activates gene transcription.

10. **PRO382**

20 Proteases are enzymatic proteins which are involved in a large number of very important biological processes in mammalian and non-mammalian organisms. Numerous different protease enzymes from a variety of different mammalian and non-mammalian organisms have been both identified and characterized, including the serine proteases which exhibit specific activity toward various serine-containing proteins. The mammalian protease enzymes play important roles in biological processes such as, for example, protein digestion, activation, inactivation, or modulation of peptide hormone activity, and alteration of the physical properties of proteins and enzymes.

25 In light of the important physiological roles played by protease enzymes, efforts are currently being undertaken by both industry and academia to identify new, native protease homologs. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, **93**:7108-7113 (1996); U.S. Patent No. 5,536,637]. We 30 herein describe the identification of novel polypeptides having homology to serine protease enzymes, designated herein as PRO382 polypeptides.

11. **PRO545**

35 The ADAM (A Disintegrin And Metalloprotease) family of proteins of which meltrin is a member may have an important role in cell interactions and in modulating cellular responses. [see, for example, Gilpin et al., *J. Biol. Chem.*, **273**(1):157-166 (1998)]. The ADAM proteins have been implicated in carcinogenesis. Meltrin- α (ADAM12) is a myoblast gene product reported to be required for cell fusion. [Harris et al., *J. Cell. Biochem.*, **67**(1):136-142 (1997), Yagami-Hiromasa et al., *Nature*, **377**:652-656 (1995)]. The meltrins contain disintegrin and metalloprotease domains and are implicated in cell adhesive events involved in development, through the integrin-binding disintegrin

domain, but also have an anti-adhesive function through a zinc-dependent metalloprotease domain. [Alfandari et al., *Devel. Biol.*, 182(2):314-330 (1997)]. Given the medical importance of cell fusion and modulation of cellular responses in carcinogenesis and other disease mechanisms, efforts are currently being undertaken to identify new, native proteins which are involved in cell fusion and modulation of cellular responses. We describe herein the identification of a novel polypeptide which has homology to meltrin, designated herein as PRO545.

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12. PRO617

CD24 is a protein that is associated with the cell surface of a variety of different cells of the mammalian immune system, including for example, neutrophils, monocytes and some lymphocytes, for example, B lymphocytes. CD24 has been shown to be a ligand for the platelet-associated surface glycoprotein P-selectin (also known as granule 10 membrane protein-140 or GMP-140), a glycoprotein that is constitutively synthesized in both platelets and endothelial cells and becomes exposed on the surface of platelets when those cells become activated. In this way, P-selectin mediates the calcium-dependent adhesion of activated platelets and endothelial cells to the various cells of the immune system that express one or more ligands for the P-selectin molecule, particularly CD24. This mechanism allows for recruitment of immune system cells to locations where they are most needed, for example, sites of injury. Thus, 15 there is substantial interest in identifying novel polypeptides that exhibit homology to the cell surface antigens of the immune system cells. We herein describe the identification and characterization of a novel polypeptide having homology to the CD24 protein, wherein that novel polypeptide is herein designated PRO617.

13. PRO700

20 Protein-disulfide isomerase (PDI) is a catalyst of disulfide formation and isomerization during protein folding. It has two catalytic sites housed in two domains homologous to thioredoxin, one near the N terminus and the other near the C terminus. [See for example, Gilbert HF, *J.Biol.Chem.*, 47:29399-29402 (1997), Mayfield KJ, *Science*, 278:1954-1957 (1997) and Puig et al., *J.Biol.Chem.*, 52:32988-32994 (1997)]. PDI is useful for formation 25 of natural type disulfide bonds in a protein which is produced in a prokaryotic cell. (See also, U.S. Patent Nos. 5,700,659 and 5,700,678).

Thus, PDI and molecules related thereto are of interest, particularly for ability to catalyze the formation of disulfide bonds. Moreover, these molecules are generally of interest in the study of redox reactions and related processes. PDI and related molecules are further described in Darby, et al., *Biochemistry* 34, 11725-11735 (1995). We herein describe the identification and characterization of novel polypeptides having homology to protein disulfide 30 isomerase, designated herein as PRO700 polypeptides.

14. PRO702

Conglutinin is a bovine serum protein that was originally described as a vertebrate lectin protein and which belongs to the family of C-type lectins that have four characteristic domains, (1) an N-terminal cysteine-rich domain, 35 (2) a collagen-like domain, (3) a neck domain and (4) a carbohydrate recognition domain (CRD). Recent reports have demonstrated that bovine conglutinin can inhibit hemagglutination by influenza A viruses as a result of their lectin properties (Eda et al., *Biochem.J.* 316:43-48 (1996)). It has also been suggested that lectins such as conglutinin can function as immunoglobulin-independent defense molecules due to complement-mediated mechanisms. Thus, conglutinin has been shown to be useful for purifying immune complexes *in vitro* and for removing circulating

immune complexes from patients plasma *in vivo* (Lim et al., *Biochem. Biophys. Res. Commun.* 218:260-266 (1996)). We herein describe the identification and characterization of a novel polypeptide having homology to the conglutinin protein, designated herein as PRO702.

15. **PRO703**

Very-long-chain acyl-CoA synthetase ("VLCAS") is a long-chain fatty acid transport protein which is active in the cellular transport of long and very long chain fatty acids. [see for example, Uchida et al., *J Biochem* (Tokyo) 119(3):565-571 (1996) and Uchiyama et al., *J Biol Chem* 271(48):30360-30365 (1996). Given the biological importance of fatty acid transport mechanisms, efforts are currently being undertaken to identify new, native proteins which are involved in fatty acid transport. We describe herein the identification of a novel polypeptide which has 10 homology to VLCAS, designated herein as PRO703.

16. **PRO705**

The glypicans are a family of glycosylphosphatidylinositol (GPI)-anchored proteoglycans that, by virtue of their cell surface localization and possession of heparin sulfate chains, may regulate the responses of cells to 15 numerous heparin-binding growth factors, cell adhesion molecules and extracellular matrix components. Mutations in one glycan protein cause of syndrome of human birth defects, suggesting that the glypicans may play an important role in development (Litwack et al., *Dev. Dyn.* 211:72-87 (1998)). Also, since the glypicans may interact with the various extracellular matrices, they may also play important roles in wound healing (McGrath et al., *Pathol.* 183:251-252 (1997)). Furthermore, since glypicans are expressed in neurons and glioma cells, they may also play 20 an important role in the regulation of cell division and survival of cells of the nervous system (Liang et al., *J. Cell. Biol.* 139:851-864 (1997)). It is evident, therefore, that the glypicans are an extremely important family of proteoglycans. There is, therefore, substantial interest in identifying novel polypeptides having homology to members of the glycan family. We herein describe the identification and characterization of a novel polypeptide having homology to K-glycan, designated herein as PRO705.

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17. **PRO708**

Aryl sulfatases are enzymes that exist in a number of different isoforms, including aryl sulfatase A (ASA), aryl sulfatase B (ASB) and aryl sulfatase C (ASC), and that function to hydrolyze a variety of different aromatic sulfates. Aryl sulfatases have been isolated from a variety of different animal tissues and microbial sources and their 30 structures and functions have been extensively studied (see, e.g., Nichol and Roy, *J. Biochem.* 55:643-651 (1964)). ASA deficiency has been reported to be associated with metachromatic leukodystrophy (MLD) (Giles et al., *Prenat. Diagn.* 7(4):245-252 (1987) and Herska et al., *Am. J. Med. Genet.* 26(3):629-635 (1987)). Additionally, other groups have reported that aryl sulfatases have been found in high levels in natural killer cells of the immune system and have hypothesized a possible role for these enzymes in NK cell-mediated cellular lysis (see, e.g., Zucker-Franklin 35 et al., *Proc. Natl. Acad. Sci. USA* 80(22):6977-6981 (1983)). Given the obvious physiological importance of the aryl sulfatase enzymes, there is a substantial interest in identifying novel aryl sulfatase homolog polypeptides. We herein describe the identification and characterization of novel polypeptides having homology to the aryl sulfatases, wherein these novel polypeptides are herein designated PRO708 polypeptides.

18. **PRO320**

Fibulin-1 is a cysteine-rich, calcium-binding extracellular matrix (ECM) component of basement membranes and connective tissue elastic fibers and plasma protein, which has four isoforms, A-D, derived from alternative splicing. Fibulin-1 is a modular glycoprotein with amino-terminal anaphlatoxin-like modules followed by nine epidermal growth factor (EGF)-like modules and, depending on alternative splicing, four possible carboxyl termini.

5 Fibulin-2 is a novel extracellular matrix protein frequently found in close association with microfibrils containing either fibronectin or fibrillin. There are multiple forms of fibulin-1 that differ in their C-terminal regions that are produced through the process of alternative splicing of their precursor RNA. [see for example Tran et al., *Matrix Biol* 15(7):479-493 (1997).]

Northern and Western blotting analysis of 16 cell lines established from tumors formed in athymic mice and
10 malignant cell lines derived from patients indicate that low expression of fibulin-1D plays a role in tumor formation and invasion. [Qing et al., *Oncogene*, 18:2159-2168 (1997)]. Ovarian-cancer cells are characterized by their ability to invade freely the peritoneal cavity. It has been demonstrated that estradiol stimulates the proliferation of estrogen-receptor (ER)-positive ovarian-cancer cells, as well as expression of fibulin-1. Studies on the effect of fibulin-1 on motility of the MDA-MB231 breast-cancer cell line, indicated inhibition of haptotactic migration of MDA-MB231
15 cells, and the authors concluded that fibulin-1 can inhibit cancer cell motility *in vitro* and therefore has the potential to inhibit tumor invasion. [Hayashido et al., *Int J Cancer*, 75(4):654-658 (1998)]

Thus, fibulin, and molecules related thereto are of interest, particularly for the use of preventing cancer. Moreover, these molecules are generally of interest in the study of connective tissue and attachment molecules and related mechanisms. Fibulin and related molecules are further described in Adams, et al., *J. Mol. Biol.*, 272(2):226-36 (1997); Kiely and Shuttleworth, *Microsc. Res. Tech.*, 38(4):413-27 (1997); and *Child. J. Card. Surg.*, 12(2Supp.):131-5 (1997).

We herein describe the identification and characterization of novel polypeptides having homology to fibulin, designated herein as PRO320 polypeptides.

25 19. **PRO324**

Oxidoreductases are enzymes that catalyze a reaction in which two molecules of a compound interact so that one molecule is oxidized and the other is reduced, with a molecule of water entering the reaction. There are many different types of oxidoreductase enzymes that play very important physiological roles in the mammalian organism. Some of the most important oxidoreductases include, for example, lyases, lactases, cholesterol oxidases, and the like.

30 These enzymes play roles in such essential processes as digestion, signal transduction, maintenance of ionic homeostasis, and the like. As such, given that oxidoreductase enzymes find various essential uses in the mammalian organism, there is a substantial interest in identifying novel oxidoreductase enzyme homologs. We herein describe the identification and characterization of a novel polypeptide having homology to oxidoreductases, designated herein as PRO324.

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20. **PRO351**

Prostasin is a novel human serine proteinase purified from human seminal fluid. Immunohistochemical localization reveals that prostasin is present in epithelial cells and ducts of the prostate gland. The cDNA for prostasin has been cloned and characterized. Southern blot analysis, following a reverse transcription polymerase

chain reaction, indicates that prostasin mRNA is expressed in prostate, liver, salivary gland, kidney, lung, pancreas, colon, bronchus, renal proximal tubular cells, and prostate carcinoma LNCaP cells. Cellular localization of prostasin mRNA was identified within epithelial cells of the human prostate gland by *in situ* hybridization histochemistry. [See for example, Yu et al., *J Biol Chem.* (1994) 269(29):18843-18848, and Yu et al., *J Biol Chem.* (1994) 270(22):13483-13489].

5 Thus, prostasin, and molecules related thereto are of interest, particularly for the study, diagnosis and treatment of medical conditions involving the prostate. Prostasin and related molecules are further described in Yu et al., *Genomics* (1996) 32(3):334-340. We herein describe the identification and characterization of novel polypeptides having homology to prostasin, designated herein as PRO351 polypeptides.

10 21. **PRO352**

Butyrophilin is a milk glycoprotein that constitutes more than 40% of the total protein associated with the fat globule membrane in mammalian milk. Expression of butyrophilin mRNA has been shown to correlate with the onset of milk fat production toward the end pregnancy and is maintained throughout lactation. Butyrophilin has been identified in bovine, murine and human (see Taylor et al., *Biochim. Biophys. Acta* 1306:1-4 (1996), Ishii et al., 15 *Biochim. Biophys. Acta* 1245:285-292 (1995), Mather et al., *J. Dairy Sci.* 76:3832-3850 (1993) and Banghart et al., *J. Biol. Chem.* 273:4171-4179 (1998)) and is a type I transmembrane protein that is incorporated into the fat globulin membrane. It has been suggested that butyrophilin may play a role as the principle scaffold for the assembly of a complex with xanthine dehydrogenase/oxidase and other proteins that function in the budding and release of milk-fat globules from the apical surface during lactation (Banghart et al., *supra*).

20 Given that butyrophilin plays an obviously important role in mammalian milk production, there is substantial interest in identifying novel butyrophilin homologs. We herein describe the identification and characterization of a novel polypeptide having homology to butyrophilin, designated herein as PRO352.

22. **PRO381**

25 The immunophilins are a family of proteins that function as receptors for immunosuppressant drugs, such as cyclosporin A, FK506, and rapamycin. The immunophilins occur in two separate classes, (1) the FK506-binding proteins (FKBPs), which bind to FK506 and rapamycin, and (2) the cyclophilins, which bind to cyclosporin A. With regard to the FK506-binding proteins, it has been reported that the FK506/FKBP complex functions to inhibit the activity of the serine/threonine protein phosphatase 2B (calcineurin), thereby providing immunosuppressant activity 30 (Gold, *Mol. Neurobiol.* 15:285-306 (1997)). It has also been reported that the FKBP immunophilins are found in the mammalian nervous system and may be involved in axonal regeneration in the central nervous system through a mechanism that is independent of the process by which immunosuppression is achieved (Gold, *supra*). Thus, there is substantial interest in identifying novel polypeptides having homology to the FKBP immunophilins. We herein describe the identification and characterization of a novel polypeptide having homology to an FKBP immunophilin 35 protein, designated herein as PRO381.

23. **PRO386**

Mammalian cell membranes perform very important functions relating to the structural integrity and activity of various cells and tissues. Of particular interest in membrane physiology is the study of transmembrane ion

channels which act to directly control a variety of physiological, pharmacological and cellular processes. Numerous ion channels have been identified including calcium (Ca), sodium (Na) and potassium (K) channels, each of which have been analyzed in detail to determine their roles in physiological processes in vertebrate and insect cells.

One type of cell membrane-associated ion channel, the sodium channel, plays an extremely important role in a cell's ability to maintain ionic homeostasis as well as transmit intracellular and extracellular signals. Voltage-gated sodium channels in brain neurons have been shown to be complexes of a pore-forming alpha unit with smaller beta-1 and beta-2 subunits (Isom et al., *Cell* 83:433-442 (1995)). Given the obvious importance of sodium channels in cellular homeostasis and other important physiological functions, there is a significant interest in identifying novel polypeptides having homology to sodium channel subunits. We herein describe the identification and characterization of a novel polypeptide having homology to the beta-2 subunit of the rat sodium channel, designated herein as PRO386.

24. **PRO540**

Lecithin-cholesterol acyltransferase ("LCAT"), also known as phosphatidylcholine-sterol acyltransferase is a key enzyme in the intravascular metabolism of high density lipoproteins, specifically in the process of cholesterol metabolism. [see, for example, Brousseau et al., *J. Lipid Res.*, 38(12):2537-2547 (1997), Hill et al., *Biochem. J.*, 294:879-884 (1993), and Drayna et al., *Nature* 327 (6123):632-634 (1987)]. Given the medical importance of lipid metabolism, efforts are currently being undertaken to identify new, native proteins which are involved in lipid transport. We describe herein the identification of a novel polypeptide which has homology to LCAT, designated herein as PRO540.

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25. **PRO615**

Synaptogyrin is a synaptic vesicle protein that is uniformly distributed in the nervous system. The cDNA encoding synaptogyrin has been cloned and sequenced and the sequence predicts a protein with a molecular mass of 25,900 D with four membrane-spanning domains. Synaptogyrin has been implicated in membrane traffic to and from the plasma membrane. Stenius et al., *J. Cell. Biol.* 131(6-2):1801-1809 (1995). In addition, a novel isoform of synaptogyrin called cellugyrin exhibits sequence identity with synaptogyrin. In rat tissues, cellugyrin and synaptogyrins are expressed in mirror image patterns. Cellugyrin is ubiquitously present in all tissues tested with the lowest levels in brain tissue, whereas synaptogyrin protein is only detectable in brain. In rat tissues, cellugyrin and synaptogyrins are expressed in mirror image patterns. The synaptic vesicle protein synaptogyrin may be a specialized version of a ubiquitous protein, cellugyrin, with the two proteins sharing structural similarity but differing in localization. This finding supports the emerging concept of synaptic vesicles as the simplified and specialized form of a generic trafficking organelle. [Janz et al., *J. Biol. Chem.* 273(5):2851-2857 (1998)] . The sequence for cellugyrin derived from the Norway rat, *Rattus norvegicus* has been deposited in the Genbank database on December 1997, designated accession number AF039085. See also, Janz et al., *J. Biol. Chem.* 273 (1998), in press.

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Given the medical importance of synaptic transmission, efforts are currently being undertaken to identify new, native proteins that may be part of a simplified and specialized generic trafficking organelle in the form of synaptic vesicles. We describe herein the identification of a novel polypeptide which has homology to synaptogyrin, designated herein as PRO615.

26. PRO618

Enteropeptidase is a key enzyme in the intestinal digestion cascade specifically cleaves the acidic propeptide from trypsinogen to yield active trypsin. This cleavage initiates a cascade of proteolytic reactions leading to the activation of many pancreatic zymogens.

See, for example, Matsushima et al., *J. Biol. Chem.* 269(31):19976-19982 (1994), Kitamoto et al., *Proc. Nat. Acad. Sci.*, 91(16):7588-7592 (1994). Enterokinase (enteropeptidase) is a related to mammalian serine proteases involved in digestion, coagulation, and fibrinolysis. LaVallie et al., *J. Biol. Chem.*, 268(31):23311-23317 (1993).

Given the medical importance of digestive processes, efforts are currently being undertaken to identify new, native proteins that may be involved in digestion, coagulation, and fibrinolysis. We describe herein the identification of a novel polypeptide which has homology to enteropeptidase, designated herein as PRO618.

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27. PRO719

Lipoprotein lipase is a key enzyme that mediates the hydrolysis of triglycerides and phospholipids present in circulating plasma lipoproteins (Dugi et al., *J. Biol. Chem.*, 270:25396-25401 (1995)). Moreover, lipoprotein lipase has been shown to mediate the uptake of lipoproteins into cells, wherein cellular uptake of lipoproteins is initiated by binding of lipoprotein lipase to cell surface proteoglycans and to the low density lipoprotein (LDL) receptor-related protein (Krapp et al., *J. Lipid Res.* 36:2362-2373 (1995)). Thus, it is clear that lipoprotein lipase plays an extremely important role in lipoprotein and cholesterol metabolism. There is, therefore, substantial interest in identifying novel polypeptides that share sequence homology and/or biological activity with lipoprotein lipase. We herein describe the identification and characterization of a novel polypeptide having sequence homology to lipoprotein lipase H, designated herein as PRO719.

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28. PRO724

The low density lipoprotein (LDL) receptor is a membrane-bound protein that plays a key role in cholesterol homeostasis, mediating cellular uptake of lipoprotein particles by high affinity binding to its ligands, apolipoprotein (apo) B-100 and apoE. The ligand-binding domain of the LDL receptor contains 7 cysteine-rich repeats of approximately 40 amino acids, wherein each repeat contains 6 cysteines, which form 3 intra-repeat disulfide bonds. These unique structural features provide the LDL receptor with its ability to specifically interact with apo B-100 and apoE, thereby allowing for transport of these lipoprotein particles across cellular membranes and metabolism of their components. Soluble fragments containing the extracellular domain of the LDL receptor have been shown to retain the ability to interact with its specific lipoprotein ligands (Simmons et al., *J. Biol. Chem.*, 272:25531-25536 (1997)). Thus, it is clear that the LDL receptor is intimately involved in important physiological activities related to cholesterol metabolism. As such, there is substantial interest in identifying novel LDL receptor homolog proteins. We herein describe the identification and characterization of a novel polypeptide having homology to the human LDL receptor protein, designated herein as PRO724..

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29. PRO772

Expression of the human gene A4 is enriched in the colonic epithelium and is transcriptionally activated on differentiation of colonic epithelial cells in vitro (Oliva et al., *Arch. Biochem. Biophys.*, 302:183-192 (1993) and Oliva et al., *Am. J. Physiol.*, 272:C957-C965 (1997)). A4 cDNA contains an open reading frame that predicts a polypeptide

of approximately 17 kilodaltons in size. Hydropathy analysis of the A4 protein revealed four putative membrane-spanning alpha-helices. Immunocytochemical studies of cells expressing A4 protein indicated that expression is localized to the endoplasmic reticulum. The four membrane-spanning domains and the biophysical characteristics of the A4 protein suggest that it belongs to a family of integral membrane proteins called proteolipids, some of which multimerize to form ion channels. In fact, preliminary evidence has suggested that A4 may itself multimerize and 5 take on the properties of an ion channel (Oliva et al., *Am. J. Physiol.*, 272:C957-C965 (1997)). Given the importance of ion channels in maintaining cellular homeostasis, there is a significant interest in identifying novel polypeptides having homology to known and putative ion channels. We herein describe the identification and characterization of a novel polypeptide having homology to the putative ion channel protein, A4, designated herein as PRO772.

10 30. **PRO852**

Proteases are enzymatic proteins which are involved in a large number of very important biological processes in mammalian and non-mammalian organisms. Numerous different protease enzymes from a variety of different mammalian and non-mammalian organisms have been both identified and characterized. The mammalian protease enzymes play important roles in many different biological processes including, for example, protein 15 digestion, activation, inactivation, or modulation of peptide hormone activity, and alteration of the physical properties of proteins and enzymes.

In light of the important physiological roles played by protease enzymes, efforts are currently being undertaken by both industry and academia to identify new, native protease homologs. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel 20 secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. We herein describe the identification of novel polypeptides having homology to various protease enzymes, designated herein as PRO852 polypeptides.

25 31. **PRO853**

Studies have reported that the redox state of the cell is an important determinant of the fate of the cell. Furthermore, reactive oxygen species have been reported to be cytotoxic, causing inflammatory disease, including tissue necrosis, organ failure, atherosclerosis, infertility, birth defects, premature aging, mutations and malignancy. Thus, the control of oxidation and reduction is important for a number of reasons, including the control and 30 prevention of strokes, heart attacks, oxidative stress, hypertension and may be associated with the development of malignancies. The levels of antioxidant enzymes, such as reductases, which catalyze the conversion of reactive oxygen species to water have been shown to be low in cancer cells. In particular, malignant prostate epithelium may have lowered expression of such antioxidant enzymes [Baker et al., *Prostate* 32(4):229-233 (1997)]. In this regard, reductases, are of interest. In addition, the transcription factors, NF-kappa B and AP-1, are known to be regulated 35 by redox state and to affect the expression of a large variety of genes thought to be involved in the pathogenesis of AIDS, cancer, atherosclerosis and diabetic complications. Publications further describing this subject matter include Engman et al., *Anticancer Res. (Greece)*, 17:4599-4605 (1997), Kelsey, et al., *Br. J. Cancer*, 76(7):852-4 (1997); Friedrich and Weiss, *J. Theor. Biol.*, 187(4):529-40 (1997) and Pieulle, et al., *J. Bacteriol.*, 179(18):5684-92 (1997). Given the physiological importance of redox reactions *in vivo*, efforts are currently being undertaken to identify new,

native proteins which are involved in redox reactions. We describe herein the identification of a novel prostate specific polypeptide which has sequence similarity to reductase, designated herein as PRO853.

32. **PRO860**

Neurofascin is a member of the L1 subgroup of the cellular adhesion molecule ("CAM") family of nervous system adhesion molecules and is involved in cellular aggregation. Cell-cell recognition and patterning of cell contacts have a critical role in mediating reversible assembly of a wide variety of transcellular complexes in the nervous system. Cell interactions may be regulated through modulation of ankyrin binding to neurofascin. See, for example, Tuvia et al., *Proc. Nat Acad. Sci.*, 94(24) 12957-12962 (1997). Neurofascin has been described as a member of the L1 subgroup of the immunoglobulin superfamily implicated in neurite extension during embryonic development for which numerous isoforms have been detected at various stages of development. See also Hassel et al., *J. Biol. Chem.*, 272(45) 28742-28749 (1997), Grumet., *Cell. Tissue Res.*, 290(2) 423-428 (1997), Garver et al., *J. Cell. Biol.*, 137:703-714 (1997), and Lambert et al., *J. Neurosci.*, 17:7025-7-36 (1997),.

Given the physiological importance of cellular adhesion molecules and development of the nervous system *in vivo*, efforts are currently being undertaken to identify new, native proteins which are involved in regulation of cellular interactions in the nervous system. We describe herein the identification and characterization of a novel polypeptide which has sequence similarity to neurofascin, designated herein as PRO860.

33. **PRO846**

The CMRF35 monoclonal antibody was used to identify a cell membrane antigen, designated CMRF35, which is present on the surface of monocytes, neutrophils, a proportion of peripheral blood T and B lymphocytes and lymphocytic cell lines. The CMRF35 cDNA encodes a novel integral membrane glycoprotein member of the immunoglobulin (Ig) gene superfamily. The molecule comprises (a) a single extracellular Ig variable domain remarkably similar to the Fc receptor for polymeric IgA and IgM, (b) a membrane-proximal domain containing a high proportion of proline, serine and threonine residues that was predicted to be heavily O-glycosylated, (c) an unusual transmembrane anchor that contained a glutamic acid and a proline residue and (d) a short cytoplasmic tail. Transcripts encoding the CMRF35 protein have been detected in early monocytic cell lines, in peripheral blood T cells and in some B lymphoblastoid cell lines, confirming the results of immunocytochemical staining. Jackson et al., *Eur. J. Immunol.* 22(5):1157-1163 (1992). CMRF-35 molecules are differentially expressed in hematopoietic cells, and the expression of the antigen was shown to be markedly influenced by stimulation with mitogens and cytokines. See, for example, Clark et al., *Exp. Hematol.* 25(8):759 (1997), Daish et al., *Immunol.* 79(1):55-63 (1993), and Clark et al., *Tissue Antigens* 48:461 (1996).

Given the physiological importance of the immune system and antigens associated with various immune system cells, efforts are currently being undertaken to identify new, native proteins which are expressed on various cells of the immune system. We describe herein the identification of a novel polypeptide which has sequence similarity to CMRF35, designated herein as PRO846.

34. **PRO862**

Lysozyme is a protein which is widely distributed in several human tissues and secretions including milk, tears and saliva. It has been demonstrated to hydrolyze linkages between N-acetylglucosamines. It has been

demonstrated to be an inhibitor of chemotaxis and of the production of toxic oxygen free radicals and may also have some role in the calcification process. As such, there is substantial interest in identifying novel polypeptides having homology to lysozyme. We describe herein the identification of a novel polypeptide which has sequence similarity to lysozyme.

5 35. **PRO864**

Wnt-4 is a secreted glycoprotein which correlates with, and is required for, kidney tubulogenesis. Mice lacking Wnt-4 activity fail to form pretubular cell aggregates; however, other aspects of mesenchymal and ureteric development are unaffected. Thus, Wnt-4 appears to act as an autoinducer of the mesenchyme to epithelial transition that underlies nephron development. Stark et al., *Nature* ;372(6507):679-683 (1994). In addition, members of the 10 Wnt gene family code for cysteine-rich, secreted proteins, which are differentially expressed in the developing brain and possibly act as intercellular signaling molecules. A Wnt gene, e.g., Wnt-1 is known to be essential for specification of the midbrain cell fate. Yoshioka et al., *Biochem. Biophys. Res. Commun.* 203(3):1581-1588 (1994). Several member of the Wnt family of secreted factors are strongly implicated as regulators of mammary cellular growth and differentiation. Shimizu et al., *Cell Growth Differ.* 8(12) 1349-1358. Wnt-4 is normally expressed in 15 early pregnancy. Wnt-4 may therefore be a local signal driving epithelial branching in pregnancy. Edwards PA, *Biochem Soc Symp.* 63:21-34 (1998). See also, Lipschutz JH, *Am. J. Kidney Dis.* 31(3):383-397, (1998). We describe herein the identification and characterizaton of a novel polypeptide which has sequence similarity to Wnt-4, designated herein as PRO864.

20 36. **PRO792**

At least two cell-derived signals have been shown to be necessary for the induction of immunoglobulin isotype switching in B-cells. The first signal is given by either of the soluble lymphokines, interleukin (IL)-4 or IL-13, which induce germline epsilon transcript expression, but this alone is insufficient to trigger secretion of immunoglobulin E (IgE). The second signal is provided by a physical interaction between B-cells and activated T-cells, basophils and mast cells, and it has been shown that the CD40/CD40 ligand pairing is crucial for mediating IgE synthesis. Additionally, amongst the numerous pairs of surface adhesion molecules that are involved in IgE synthesis, the CD23/CD21 pair appears to play a key role in the generation of IgE. CD23 is a protein that is positively and negatively regulated by factors which increase or decrease IgE production, respectively. Antibodies to CD23 have been shown to inhibit IL-4-induced human IgE production *in vitro* and to inhibit antigen-specific IgE 25 responses in a rat model, in an isotype selective manner (Bonnefoy et al., *Eur. Respir. J. Suppl.* 22:63S-66S (1996)). CD23 interacts with CD21 on B-cells, preferentially driving IgE production. Given that the CD23 protein plays an extremely important role in the induction of a mammalian IgE response, there is significant interest in identifying 30 novel polypeptides having homology to CD23. We herein describe the identification and characterization of a novel polypeptide having homology to CD23, designated herein as PRO792.

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37. **PRO866**

Mindin and spondin proteins are secreted proteins that are structurally related to one another and which have been identified in a variety of organisms. For example, Higashijima et al., *Dev. Biol.* 192:211-227 (1997) have reported the identification of spondin and mindin expression in floor plate cells in the zebrafish embryonic axis,

thereby suggesting that mindin and spondin proteins play important roles in embryonic development. This same group has reported that mindin and spondin proteins function as extracellular matrix proteins that have a high affinity for the basal lamina. (Id.). It has been reported that F-spondin is a secreted protein that promotes neural adhesion and neurite extension (Klar et al., *Cell* 69:95-110 (1992) and that M-spondin is an extracellular matrix protein that localizes to muscle attachment sites in Drosophila (Umemiya et al., *Dev. Biol.* 186:165-176 (1997)). Thus, there
5 is significant interest in identifying novel polypeptides having homology to the mindin and spondin proteins. We herein describe the identification and characterization of a novel polypeptide having homology to mindin2 and mindin1, designated herein as PRO866.

38. **PRO871**

10 Cyclophilins are a family of proteins that bind to cyclosporin A and possess peptidyl-prolyl cis-trans isomerase activity (Sherry et al., *Proc. Natl. Acad. Sci. USA* 95:1758-1763 (1998)). In addition, cyclophilins are secreted by activated cells and act in a cytokine-like manner, presumably via signaling through a cell surface cyclophilin receptor. Host cell-derived cyclophilin A has been shown to be incorporated into HIV-1 virions and its incorporation has been shown to be essential for viral infectivity. Thus, one or more the cyclophilins may be directly
15 associated with HIV-1 infectivity. Given the obvious importance of the cyclophilin proteins, there is substantial interest in identifying novel polypeptides which have sequence homology to one or more of the cyclophilin proteins. We herein describe the identification and characterization of a novel polypeptide having homology to cyclophilin-like protein CyP-60, designated herein as PRO871.

20 39. **PRO873**

Enzymatic proteins play important roles in the chemical reactions involved in the digestion of foods, the biosynthesis of macromolecules, the controlled release and utilization of chemical energy, and other processes necessary to sustain life. Enzymes have also been shown to play important roles in combating various diseases and disorders. For example, liver carboxylesterases have been reported to assist in sensitizing human tumor cells to the
25 cancer prodrugs. Danks et al., report that stable expression of the cDNA encoding a carboxylesterase in Rh30 human rhabdomyosarcoma cells increased the sensitivity of the cells to the CPT-11 cancer prodrug 8.1-fold. *Cancer Res.* (1998) 58(1):20-22. The authors propose that this prodrug/enzyme combination could be exploited therapeutically in a manner analogous to approaches currently under investigation with the combinations of ganciclovir/herpes simplex virus thymidine kinase and 5-fluorocytosine/cytosine deaminase. van Pelt et al. demonstrated that a 55 kD
30 human liver carboxylesterase inhibits the invasion of *Plasmodium falciparum* malaria sporozoites into primary human hepatocytes in culture. *J Hepatol* (1997) 27(4):688-698.

Carboxylesterases have also been found to be of importance in the detoxification of drugs, pesticides and other xenobiotics. Purified human liver carboxylesterases have been shown to be involved in the metabolism of various drugs including cocaine and heroin. Prindel et al. describe the purification and cloning of a broad substrate
35 specificity human liver carboxylesterase which catalyzes the hydrolysis of cocaine and heroin and which may play an important role in the degradation of these drugs in human tissues. *J. Biol. Chem.* (1997) 6:272(23):14769-14775. Brzencinski et al. describe a spectrophotometric competitive inhibition assay used to identify drug or environmental esters that are metabolized by carboxylesterases. *Drug Metab Dispos* (1997) 25(9):1089-1096.

In light of the important physiological roles played by carboxylesterases, efforts are being undertaken by both industry and academia to identify new, native carboxylesterase homologs. We herein describe the identification and characterization of a novel polypeptide having homology to carboxylesterase, designated herein as PRO873.

40. **PRO940**

CD33 is a cell-surface protein that is a member of the sialoadhesin family of proteins that are capable of mediating sialic-acid dependent binding with distinct specificities for both the type of sialic acid and its linkage to subterminal sugars. CD33 is specifically expressed in early myeloid and some monocyte cell lineages and has been shown to be strongly associated with various myeloid tumors including, for example, acute non-lymphocytic leukemia (ANLL). As such, CD33 has been suggested as a potential target for the treatment of cancers associated with high level expression of the protein. There is, therefore, significant interest in the identification of novel polypeptides having homology to CD33. In fact, one CD33 homolog (designated CD33L) has already been identified and described (see Takei et al., *Cytogenet. Cell Genet.* 78:295-300 (1997)). We herein describe the identification of another novel polypeptide having homology to CD33, designated herein as PRO940. The novel polypeptide described herein also exhibits significant homology to the human OB binding proteins designated HSU71382_1 and HSU71383_1 in the Dayhoff database (version 35.45 SwissProt 35).

41. **PRO941**

Cadherins are a large family of transmembrane proteins. Cadherins comprise a family of calcium-dependent glycoproteins that function in mediating cell-cell adhesion in virtually all solid tissues of multicellular organisms. At least cadherins 1-13 as well as types B, E, EP, M, N, P and R have been identified and characterized. Among the functions cadherins are known for, with some exceptions, are that cadherins participate in cell aggregation and are associated with cell-cell adhesion sites. Recently, it has been reported that while all cadherins share multiple repeats of a cadherin specific motif believed to correspond to folding of extracellular domains, members of the cadherin superfamily have divergent structures and, possibly, functions. In particular it has been reported that members of the cadherin superfamily are involved in signal transduction. See, Suzuki, *J. Cell Biochem.*, 61(4):531-542 (1996). Cadherins are further described in Tanihara et al., *J. Cell Sci.*, 107(6):1697-1704 (1994), Aberle et al., *J. Cell Biochem.*, 61(4):514-523 (1996) and Tanihara et al., *Cell Adhes. Commun.*, 2(1):15-26 (1994). We herein describe the identification and characterization of a novel polypeptide having homology to a cadherin protein, designated herein as PRO941.

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42. **PRO944**

Clostridium perfringens enterotoxin (CPE) is considered to be the virulence factor responsible for causing the symptoms of *C. perfringens* type A food poisoning and may also be involved in other human and veterinary illnesses (McClane, *Toxicon*, 34:1335-1343 (1996)). CPE carries out its adverse cellular functions by binding to an approximately 50 kD cell surface receptor protein designated the *Clostridium perfringens* enterotoxin receptor (CPE-R) to form an approximately 90,000 kD complex on the surface of the cell. cDNAs encoding the CPE-R protein have been identified characterized in both human and mouse (Katahira et al., *J. Cell Biol.* 136:1239-1247 (1997) and Katahira et al., *J. Biol. Chem.* 272:26652-26658 (1997)). Since the CPE toxin has been reported to cause a variety of illnesses in mammalian hosts and those illnesses are initiated by binding of the CPE toxin to the CPE-R, there is

significant interest in identifying novel CPE-R homologs. We herein describe the identification and characterization of a novel polypeptide having homology to the CPE-R, designated herein as PRO944.

43. PRO983

Membrane-bound proteins include not only cell-surface membrane-bound proteins, but also proteins that are found on the surface of intracellular vesicles. These vesicles are involved in exocytosis, which is the fusion of secretory vesicles with the cellular plasma membrane, and have two main functions. One is the discharge of the vesicle contents into the extracellular space, and the second is the incorporation of new proteins and lipids into the plasma membrane itself. Exocytosis can be either constitutive or regulated. All eukaryotic cells exhibit constitutive exocytosis, which is marked by the immediate fusion of the secretory vesicle after formation. In contrast, regulated exocytosis results in the accumulation of the secretory vesicles that fuse with the plasma membrane upon receipt of an appropriate signal by vesicle-associated membrane proteins. Usually, this signal is an increase in the cytosolic free Ca^{2+} concentration. However, regulated exocytosis that is independent of Ca^{2+} has been reported (see, e.g. Fujita-Yoshigaki *et al.* J. Biol. Chem. (1996) 31:271(22):13130-13134). Regulated exocytosis is crucial to many specialized cells, including neurons (neurotransmitter release from synaptic vesicles), adrenal chromaffin cells (adrenaline secretion), pancreatic acinar cells (digestive enzyme secretion), pancreatic β -cells (insulin secretion), mast cells (histamine secretion), mammary cells (milk protein secretion), sperm (enzyme secretion), egg cells (creation of fertilization envelope) and adipocytes (insertion of glucose transporters into the plasma membrane).

Disorders involving exocytosis are known. For example, inflammatory mediator release from mast cells leads to a variety of disorders, including asthma. Similarly, Chediak-Higashi Syndrome (CHS) is a rare autosomal recessive disease in which neutrophils, monocytes and lymphocytes contain giant cytoplasmic granules. Accordingly, the proteins involved in exocytosis are of paramount interest and efforts are being undertaken by both industry and academia to identify new, vesicle-associated proteins. For example, Skehel *et al.* identified a 33-kilodalton membrane protein in Aplysia, termed VAP-33, which is required for the exocytosis of neurotransmitter. Science (1995) 15:269(5230):1580-1583, and Neuropharmacology (1995) 34(11):1379-1385. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel vesicle-associated membrane proteins. It is an object of the invention to provide proteins having homology to the vesicle associated protein, VAP-33, designated herein as PRO983.

44. PRO1057

Proteases are enzymatic proteins which are involved in a large number of very important biological processes in mammalian and non-mammalian organisms. Numerous different protease enzymes from a variety of different mammalian and non-mammalian organisms have been both identified and characterized. The mammalian protease enzymes play important roles in many different biological processes including, for example, protein digestion, activation, inactivation, or modulation of peptide hormone activity, and alteration of the physical properties of proteins and enzymes.

In light of the important physiological roles played by protease enzymes, efforts are currently being undertaken by both industry and academia to identify new, native protease homologs. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example,

Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. We herein describe the identification of novel polypeptides having homology to various protease enzymes, designated herein as PRO1057 polypeptides.

45. PRO1071

Thrombospondin-1 is a trimeric high molecular weight glycoprotein that is released from platelet alpha-granules in response to thrombin stimulation and that is also a transient component of the extracellular matrix in developing and repairing tissues (Adams, Int. J. Biochem. Cell Biol. 29:861-865 (1997) and Qian et al., Proc. Soc. Exp. Biol. Med. 212:199-207 (1996)). A variety of factors regulate thrombospondin expression and the protein is degraded by both extracellular and intracellular routes. Thrombospondin-1 functions as a cell adhesion molecule and also modulates cell movement, cell proliferation, neurite outgrowth and angiogenesis. As such, there is substantial interest in identifying novel polypeptides having homology to thrombospondin. We herein describe the identification and characterization of a novel polypeptide having homology to thrombospondin, designated herein as PRO1071.

46. PRO1072

Studies have reported that the redox state of the cell is an important determinant of the fate of the cell. Furthermore, reactive oxygen species have been reported to be cytotoxic, causing inflammatory disease, including tissue necrosis, organ failure, atherosclerosis, infertility, birth defects, premature aging, mutations and malignancy. Thus, the control of oxidation and reduction is important for a number of reasons, including the control and prevention of strokes, heart attacks, oxidative stress, hypertension and may be associated with the development of malignancies. The levels of antioxidant enzymes, such as reductases, which catalyze the conversion of reactive oxygen species to water have been shown to be low in cancer cells. In particular, malignant prostate epithelium may have lowered expression of such antioxidant enzymes [Baker et al., Prostate 32(4):229-233 (1997)]. In this regard, reductases, are of interest. In addition, the transcription factors, NF-kappa B and AP-1, are known to be regulated by redox state and to affect the expression of a large variety of genes thought to be involved in the pathogenesis of AIDS, cancer, atherosclerosis and diabetic complications. Publications further describing this subject matter include Engman et al., Anticancer Res. (Greece), 17:4599-4605 (1997), Kelsey, et al., Br. J. Cancer, 76(7):852-854 (1997); Friedrich and Weiss, J. Theor. Biol., 187(4):529-40 (1997) and Pieulle, et al., J. Bacteriol., 179(18):5684-92 (1997). Given the physiological importance of redox reactions *in vivo*, efforts are currently being undertaken to identify new, native proteins which are involved in redox reactions. We describe herein the identification of a novel polypeptide which has sequence similarity to reductase enzymes, designated herein as PRO1072.

47. PRO1075

Protein disulfide isomerase is an enzymatic protein which is involved in the promotion of correct refolding of proteins through the establishment of correct disulfide bond formation. Protein disulfide isomerase was initially identified based upon its ability to catalyze the renaturation of reduced denatured RNase (Goldberger et al., J. Biol. Chem. 239:1406-1410 (1964) and Epstein et al., Cold Spring Harbor Symp. Quant. Biol. 28:439-449 (1963)). Protein disulfide isomerase has been shown to be a resident enzyme of the endoplasmic reticulum which is retained in the endoplasmic reticulum via a -KDEL or -HDEL amino acid sequence at its C-terminus.

Given the importance of disulfide bond-forming enzymes and their potential uses in a number of different

applications, for example in increasing the yield of correct refolding of recombinantly produced proteins, efforts are currently being undertaken by both industry and academia to identify new, native proteins having homology to protein disulfide isomerase. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel protein disulfide isomerase homologs. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); 5 U.S. Patent No. 5,536,637)]. We herein describe a novel polypeptide having homology to protein disulfide isomerase, designated herein as PRO1075.

48. **PRO181**

In Drosophila, the dorsal-ventral polarity of the egg chamber depends on the localization of the oocyte nucleus and the gurken RNA to the dorsal-anterior corner of the oocyte. Gurken protein presumably acts as a ligand for the drosophila EGF receptor (torpedo/DER) expressed in the somatic follicle cells surrounding the oocyte. Cornichon is a gene required in the germline for dorsal-ventral signaling (Roth et al., *Cell* 81:967-978 (1995)). Cornichon, gurken and torpedo also function in an earlier signaling event that establishes posterior follicle cell fates and specifies the anterior-posterior polarity of the egg chamber. Mutations in any or all of these genes prevent the formation of a correctly polarized microtubule cytoskeleton required for proper localization of the anterior and posterior determinants bicoid and oskar and for the asymmetric positioning of the oocyte nucleus. Thus, it is clear that the cornichon gene product plays an important role in early development. We herein describe the identification and characterization of a novel polypeptide having homology to the cornichon protein, designated herein as PRO181.

20 49. **PRO195**

Efforts are currently being undertaken to identify and characterize novel transmembrane proteins. We herein describe the identification and characterization of a novel transmembrane polypeptide, designated herein as PRO195.

25 50. **PRO865**

Efforts are currently being undertaken to identify and characterize novel secreted proteins. We herein describe the identification and characterization of a novel secreted polypeptide, designated herein as PRO865.

51. **PRO827**

30 VLA-2 is an cell-surface integrin protein that has been identified and characterized in a number of mammalian organisms, including both mouse and human. VLA-2 has been shown to be a receptor on the surface of cells for echovirus-1 (EV-1) which mediates infection of VLA-2-expressing cells by EV-1 (Zhang et al., *Virology* 235(2):293-301 (1997) and Bergelson et al., *Science* 255:1718-1720 (1992)). VLA-2 has also been shown to mediate the interaction of collagen with endothelium during *in vitro* vascular tube formation (Jackson et al., *Cell Biol. Int.* 18(9):859-867 (1994)). Various other integrin proteins that share various degrees of amino acid sequence homology with VLA-2 have been identified and characterized in a variety of mammalian organism. These integrins have been reported to play important roles in a variety of different physiological functions. Therefore, there is significant interest in identifying novel polypeptides having homology to one or more of the integrin proteins. We herein describe the identification and characterization of a novel polypeptide having homology to VLA-2 integrin protein,

designated herein as PRO827.

52. **PRO1114**

Many important cytokine proteins have been identified and characterized and shown to signal through specific cell surface receptor complexes. For example, the class II cytokine receptor family (CRF2) includes the 5 interferon receptors, the interleukin-10 receptor and the tissue factor CRFB4 (Spencer et al., J. Exp. Med. 187:571-578 (1998) and Kotenko et al., EMBO J. 16:5894-5903 (1997)). Thus, the multitude of biological activities exhibited by the various cytokine proteins is absolutely dependent upon the presence of cytokine receptor proteins on the surface of target cells. There is, therefore, a significant interest in identifying and characterizing novel polypeptides having homology to one or more of the cytokine receptor family. We herein describe the identification and 10 characterization of a novel polypeptide having homology to cytokine receptor family-4 proteins, designated herein as PRO1117.

Interferons (IFNs) encompass a large family of secreted proteins occurring in vertebrates. Although they were originally named for their antiviral activity, growing evidence supports a critical role for IFNs in cell growth and differentiation (Jaramillo et al., Cancer Investigation 13(3):327-338 (1995)). IFNs belong to a class of negative 15 growth factors having the ability to inhibit the growth of a wide variety of cells with both normal and transformed phenotypes. IFN therapy has been shown to be beneficial in the treatment of human malignancies such as Karposi's sarcoma, chronic myelogenous leukemia, non-Hodgkin's lymphoma, and hairy cell leukemia as well as in the treatment of infectious diseases such as hepatitis B (Gamliel et al., Scanning Microscopy 2(1):485-492 (1988), Einhorn et al., Med. Oncol. & Tumor Pharmacother. 10:25-29 (1993), Ringenberg et al., Missouri Medicine 20 85(1):21-26 (1988), Saracco et al., Journal of Gastroenterology and Hepatology 10:668-673 (1995), Gonzalez-Mateos et al., Hepato-Gastroenterology 42:893-899 (1995) and Malaguarnera et al., Pharmacotherapy 17(5):998-1005 (1997)).

Interferons can be classified into two major groups based upon their primary sequence. Type I interferons, IFN- α and IFN- β , are encoded by a superfamily of intronless genes consisting of the IFN- α gene family and a single 25 IFN- β gene that are thought to have arisen from a common ancestral gene. Type I interferons may be produced by most cell types. Type II IFN, or IFN- γ , is restricted to lymphocytes (T cells and natural killer cells) and is stimulated by nonspecific T cell activators or specific antigens *in vivo*.

Although both type I and type II IFNs produce similar antiviral and antiproliferative effects, they act on distinct cell surface receptors, wherein the binding is generally species specific (Langer et al., Immunol. Today 9:393-30 400 (1988)). Both IFN- α and IFN- β bind competitively to the same high affinity type I receptor, whereas IFN- γ binds to a distinct type II receptor. The presence and number of IFN receptors on the surface of a cell does not generally reflect the sensitivity of the cell to IFN, although it is clear that the effects of the IFN protein is mediated through binding to a cell surface interferon receptor. As such, the identification and characterization of novel interferon receptor proteins is of extreme interest.

35 We herein describe the identification and characterization of novel interferon receptor polypeptides, designated herein as "PRO1114 interferon receptor" polypeptides. Thus, the PRO1114 polypeptides of the present invention represents a novel cell surface interferon receptor.

53. PRO237

Carbonic anhydrase is an enzymatic protein that which aids carbon dioxide transport and release in the mammalian blood system by catalyzing the synthesis (and the dehydration) of carbonic acid from (and to) carbon dioxide and water. Thus, the actions of carbonic anhydrase are essential for a variety of important physiological reactions in the mammal. As such, there is significant interest in the identification and characterization of novel 5 polypeptides having homology to carbonic anhydrase. We herein describe the identification and characterization of a novel polypeptide having homology to carbonic anhydrase, designated herein as PRO237.

54. PRO541

Numerous trypsin inhibitory proteins have been identified and characterized (see, e.g., Yamakawa et al., 10 *Biochim. Biophys. Acta* 1395:202-208 (1998) and Mizuki et al., *Mammalian Genome* 3:274-280 (1992)). Trypsin inhibitor proteins play important roles in a variety of different physiological and biological pathways and are specifically involved in such processes as the regulation of protein degradation, digestion, and the like. Given the important roles played by such enzymatic proteins, there is significant interest in identifying and characterizing novel polypeptides having homology to known trypsin inhibitor proteins. We herein describe the identification and 15 characterization of a novel polypeptide having homology to a trypsin inhibitor protein, designated herein as PRO541.

55. PRO273

Leukocytes include monocytes, macrophages, basophils, and eosinophils and play an important role in the immune response. These cells are important in the mechanisms initiated by T and/or B lymphocytes and secrete a 20 range of cytokines which recruit and activate other inflammatory cells and contribute to tissue destruction.

Thus, investigation of the regulatory processes by which leukocytes move to their appropriate destination and interact with other cells is critical. Currently, leukocytes are thought to move from the blood to injured or inflamed tissues by rolling along the endothelial cells of the blood vessel wall. This movement is mediated by transient interactions between selectins and their ligands. Next, the leukocyte must move through the vessel wall and 25 into the tissues. This diapedesis and extravasation step involves cell activation which promotes a more stable leukocyte-endothelial cell interaction, again mediated by integrins and their ligands.

Chemokines are a large family of structurally related polypeptide cytokines. These molecules stimulate leukocyte movement and may explain leukocyte trafficking in different inflammatory situations. Chemokines mediate the expression of particular adhesion molecules on endothelial cells, and they produce chemoattractants which activate 30 specific cell types. In addition, the chemokines stimulate proliferation and regulate activation of specific cell types. In both of these activities, chemokines demonstrate a high degree of target cell specificity.

The chemokine family is divided into two subfamilies based on whether two amino terminal cysteine residues are immediately adjacent (C-C) or separated by one amino acid (C-X-C). Chemokines of the C-X-C family generally activate neutrophils and fibroblasts while the C-C chemokines act on a more diverse group of target cells including 35 monocytes/macrophages, basophils, eosinophils and T lymphocytes. The known chemokines of both subfamilies are synthesized by many diverse cell types as reviewed in Thomson A. (1994) *The Cytokine Handbook*, 2 d Ed. Academic Press, N.Y. Chemokines are also reviewed in Schall TJ (1994) *Chemotactic Cytokines: Targets for Therapeutic Development*. International Business Communications, Southborough Mass. pp 180-270; and in Paul WE (1993) *Fundamental Immunology*, 3rd Ed. Raven Press, N.Y. pp 822-826.

Known chemokines of the C-X-C subfamily include macrophage inflammatory proteins alpha and beta (MIP-1 and MIP-2), interleukin-8 (IL-8), and growth regulated protein (GRO-alpha and beta).

MIP-2 was first identified as a 6 kDa heparin binding protein secreted by the mouse macrophage cell line RAW 264.7 upon stimulation with lipopolysaccharide (LPS). MIP-2 is a member of the C-X-C (or CXC) subfamily of chemokines. Mouse MIP-2 is chemotactic for human neutrophils and induces local neutrophil infiltration when injected into the foot pads of mice. Rat MIP-2 shows 86% amino acid homology to the mouse MIP-2 and is chemotactic for rat neutrophils but does not stimulate migration of rat alveolar macrophages or human peripheral blood eosinophils or lymphocytes. In addition, the rat MIP-2 has been shown to stimulate proliferation of rat alveolar epithelial cells but not fibroblasts.

Current techniques for diagnosis of abnormalities in inflamed or diseased issues mainly rely on observation of clinical symptoms or serological analyses of body tissues or fluids for hormones, polypeptides or various metabolites. Problems exist with these diagnostic techniques. First, patients may not manifest clinical symptoms at early stages of disease. Second, serological tests do not always differentiate between invasive diseases and genetic syndromes. Thus, the identification of expressed chemokines is important to the development of new diagnostic techniques, effective therapies, and to aid in the understanding of molecular pathogenesis.

To date, chemokines have been implicated in at least the following conditions: psoriasis, inflammatory bowel disease, renal disease, arthritis, immune-mediated alopecia, stroke, encephalitis, MS, hepatitis, and others. In addition, non-ELR-containing chemokines have been implicated in the inhibition of angiogenesis, thus indicating that these chemokines have a role in tumor vascularization and tumorigenesis.

Therefore it is the object of this invention to identify polypeptides and nucleic acids encoding the same which have sequence identity and similarity with cytokine-induced neutrophil chemoattractants, MIP-1, MIP-2, and other related proteins. The efforts of this object are provided herein.

56. PRO701

Beta neurexins and neuroligins are plasma membrane proteins that are displayed on the neuronal cell surface. Neuroligin 1 is enriched in synaptic plasma membranes and acts as a splice site-specific ligand for beta neurexins as described in Ichitchenko, et al., *Cell*, 81(3):435-443 (1995). The extracellular sequence of neuroligin 1 is composed of a catalytically inactive esterase domain homologous to acetylcholinesterase. Neuroligin 2 and 3 are similar in structure and sequence to neuroligin 1. All neuroligins contain an N-terminal hydrophobic sequence with the characteristics of a cleaved signal peptide followed by a large esterase homology domain, a highly conserved single transmembrane region, and a short cytoplasmic domain. The three neuroligins are alternatively spliced at the same position and are expressed at high levels only in the brain. Tight binding of the three neuroligins to beta neurexins is observed only for beta neurexins lacking an insert in splice site 4. Thus, neuroligins constitute a multigene family of brain-specific proteins with distinct isoforms that may have overlapping functions in mediating recognition processes between neurons, see Ichitchenko, et al., *J. Biol. Chem.*, 271(5):2676-2682 (1996). Moreover, neurexins and neuroligins have been reported as functioning as adhesion molecules in a Ca^{2+} dependent reaction that is regulated by alternative splicing of beta neurexins, i.e., see Nguyen and Sudhof, *J. Biol. Chem.*, 272(41):26032-26039 (1997).

Given the foregoing, membrane bound proteins are of interest. More generally, membrane-bound proteins and receptors can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is

typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and 5 cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as 10 pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound 15 receptor proteins, particularly those having sequence identity and/or similarity with neuroligins 1, 2 and 3. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts are provided herein.

20 57. **PRO704**

VIP36 is localized to the Golgi apparatus and the cell surface, and belongs to a family of legume lectin 25 homologues in the animal secretory pathway that might be involved in the trafficking of glycoproteins, glycolipids, or both. It is further believed that VIP36 binds to sugar residues of glycosphingolipids and/or glycosylphosphatidyl-inositol anchors and might provide a link between the extracellular/luminal face of glycolipid rafts and the cytoplasmic protein segregation machinery. Further regarding VIP36, it is believed that there is a signal at its C-terminus that matches an internalization consensus sequence which confers its ability to cycle between the plasma membrane and Golgi. See, Fiedler, et al., *EMBO J.*, 13(7):1729-1740 (1994); Fiedler and Simons, *J. Cell Sci.*, 109(1):271-276 (1996); Itin, et al., *MBO J.*, 14(10):2250-2256 (1995). It is believed that VIP36 is either the same as or very closely related to the human GP36b protein. VIP36 and/or GP36b are of interest.

30 More generally, vesicular, cytoplasmic, extracellular and membrane-bound proteins play important roles in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and 35 hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment, usually at a membrane-bound receptor protein.

Secreted proteins have various industrial applications, including use as pharmaceuticals, diagnostics, biosensors and bioreactors. In fact, most protein drugs available at present, such as thrombolytic agents, interferons,

interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane-bound proteins, also have potential as therapeutic or diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. Membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Such membrane-bound proteins and cell receptors include, but are not limited
5 to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

10 Efforts are being undertaken by both industry and academia to identify new, native vesicular, cytoplasmic, secreted and membrane-bound receptor proteins, particularly those having sequence identity and/or similarity with VIP36. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S.
15 Patent No. 5,536,637)].

58. **PRO706**

Acid phosphatase proteins are secreted proteins which dephosphorylate terminal phosphate groups under acidic pH conditions. Acid phosphatases contain a RHGXRXP amino acid sequence, which is predicted to be mechanistically
20 significant. Acid phosphatases may have important functions in the diagnosis and treatment of human diseases. For example, prostatic acid phosphatase is a secreted protein uniquely expressed in prostatic tissue and prostate cancer. The level of prostatic acid phosphatase is a potential prognostic factor for local and biochemical control in prostate cancer patients treated with radiotherapy, as described in Lankford et al., *Int. J. Radiat. Oncol. Biol. Phys.* 38(2): 327-333 (1997). Research suggests that a cellular immune response to prostatic acid phosphatase may mediate
25 destructive autoimmune prostatitis, and that xenogeneic forms of prostatic acid phosphatase may prove useful for immunotherapy of prostate cancer. See Fong et al., *J. Immunol.* 169(7): 3113-3117 (1997). Seminal prostatic acid phosphatase levels correlate significantly with very low sperm levels (oligospermia) in individuals over 35, see Singh et al., *Singapore Med. J.* 37(6): 598-599 (1996). Thus, prostatic acid phosphatase has been implicated in a variety
30 of human diseases, and may have an important function in diagnosis and therapy of these diseases. A series of aminobenzylphosphatic acid compounds are highly potent inhibitors of prostatic acid phosphatase, as described in Beers et al., *Bioorg. Med. Chem.* 4(10): 1693-1701 (1996).

More generally, extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or
35 the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins, particularly those having sequence identity 5 with prostate acid phosphatase precursor and lysosomal acid phosphatase precursor and in some cases, those having identity with DNA found in fetal heart. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

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59. PRO707

Cadherins are a large family of transmembrane proteins. At least cadherins 1-13 as well as types B, E, EP, M, N, P and R have been characterized. Among the functions cadherins are known for, with some exceptions, cadherins participate in cell aggregation and are associated with cell-cell adhesion sites. Cadherins are further 15 described in Tanihara, et al., *J. Cell Sci.*, 107(6):1697-1704 (1994) and Tanihara, et al., *Cell Adhes. Commun.*, 2(1):15-26 (1994). Moreover, it has been reported that some members of the cadherin superfamily are involved in general cell-cell interaction processes including transduction. See, Suzuki, *J. Cell Biochem.*, 61(4):531-542 (1996). Therefore, novel members of the cadherin superfamily are of interest.

More generally, all novel proteins are of interest, including membrane-bound proteins. Membrane-bound 20 proteins and receptors can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse 25 cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast 30 growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native secreted and membrane-bound receptor proteins, particularly membrane bound proteins having identity with cadherins. The results of such 35 efforts are provided herein.

60. PRO322

Proteases are enzymatic proteins which are involved in a large number of very important biological processes in mammalian and non-mammalian organisms. Numerous different protease enzymes from a variety of different mammalian and non-mammalian organisms have been both identified and characterized, including the serine proteases which exhibit specific activity toward various serine-containing proteins. The mammalian protease enzymes 5 play important roles in biological processes such as, for example, protein digestion, activation, inactivation, or modulation of peptide hormone activity, and alteration of the physical properties of proteins and enzymes.

Neuropsin is a novel serine protease whose mRNA is expressed in the central nervous system. Mouse neuropsin has been cloned, and studies have shown that it is involved in the hippocampal plasticity. Neuropsin has also been indicated as associated with extracellular matrix modifications and cell migrations. See, generally, Chen, 10 et al., *Neurosci.*, 7(2):5088-5097 (1995) and Chen, et al., *J. Histochem. Cytochem.*, 46:313-320 (1998).

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound or secreted proteins, particularly those having homology to neuropsin, serine protease, neurosin and trypsinogen. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described 15 in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S. Patent No. 5,536,637].

61. PRO526

Protein-protein interactions include those involved with receptor and antigen complexes and signaling 20 mechanisms. As more is known about the structural and functional mechanisms underlying protein-protein interactions, protein-protein interactions can be more easily manipulated to regulate the particular result of the protein-protein interaction. Thus, the underlying mechanisms of protein-protein interactions are of interest to the scientific and medical community.

All proteins containing leucine-rich repeats are thought to be involved in protein-protein interactions. 25 Leucine-rich repeats are short sequence motifs present in a number of proteins with diverse functions and cellular locations. The crystal structure of ribonuclease inhibitor protein has revealed that leucine-rich repeats correspond to beta-alpha structural units. These units are arranged so that they form a parallel beta-sheet with one surface exposed to solvent, so that the protein acquires an unusual, nonglobular shape. These two features have been indicated as responsible for the protein-binding functions of proteins containing leucine-rich repeats. See, Kobe and 30 Deisenhofer, *Trends Biochem. Sci.*, 19(10):415-421 (Oct. 1994).

A study has been reported on leucine-rich proteoglycans which serve as tissue organizers, orienting and ordering collagen fibrils during ontogeny and are involved in pathological processes such as wound healing, tissue repair, and tumor stroma formation. Iozzo, R. V., *Crit. Rev. Biochem. Mol. Biol.*, 32(2):141-174 (1997). Others studies implicating leucine rich proteins in wound healing and tissue repair are De La Salle, C., et al., *Vox. Rev. 35 Fr. Hematol.* (Germany), 37(4):215-222 (1995), reporting mutations in the leucine rich motif in a complex associated with the bleeding disorder Bernard-Soulier syndrome, Chlemetson, K. J., *Thromb. Haemost.* (Germany), 74(1):111-116 (July 1995), reporting that platelets have leucine rich repeats and Ruoslahti, E. I., et al., WO9110727-A by La Jolla Cancer Research Foundation reporting that decorin binding to transforming growth factor β has involvement in a treatment for cancer, wound healing and scarring. Related by function to this group of proteins is the insulin like

growth factor (IGF), in that it is useful in wound-healing and associated therapies concerned with re-growth of tissue, such as connective tissue, skin and bone; in promoting body growth in humans and animals; and in stimulating other growth-related processes. The acid labile subunit (ALS) of IGF is also of interest in that it increases the half-life of IGF and is part of the IGF complex *in vivo*. ALS is further described in Leong and Baxter, Mol. Endocrinol., 6(6):870-876 (1992); Baxter, J. Biol. Chem., 264(20):11843-11848 (1989); and Khosravi, et al., J. Clin. Endocrinol. Metab., 82(12):3944-3951 (1997).

Another protein which has been reported to have leucine-rich repeats is the SLIT protein which has been reported to be useful in treating neuro-degenerative diseases such as Alzheimer's disease, nerve damage such as in Parkinson's disease, and for diagnosis of cancer, see, Artavanistsakonas, S. and Rothberg, J. M., WO9210518-A1 by Yale University. Also of interest is LIG-1, a membrane glycoprotein that is expressed specifically in glial cells in the mouse brain, and has leucine rich repeats and immunoglobulin-like domains. Suzuki, et al., J. Biol. Chem. (U.S.), 271(37):22522 (1996). Other studies reporting on the biological functions of proteins having leucine rich repeats include: Tayar, N., et al., Mol. Cell Endocrinol., (Ireland), 125(1-2):65-70 (Dec. 1996) (gonadotropin receptor involvement); Miura, Y., et al., Nippon Rinsho (Japan), 54(7):1784-1789 (July 1996) (apoptosis involvement); Harris, P. C., et al., J. Am. Soc. Nephrol., 6(4):1125-1133 (Oct. 1995) (kidney disease involvement).

Efforts are therefore being undertaken by both industry and academia to identify new proteins having leucine rich repeats to better understand protein-protein interactions. Of particular interest are those proteins having leucine rich repeats and identity or similarity to known proteins having leucine rich repeats such as ALS. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound proteins having leucine rich repeats. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637].

62. PRO531

Cadherins are a large family of transmembrane proteins. Cadherins comprise a family of calcium-dependent glycoproteins that function in mediating cell-cell adhesion in virtually all solid tissues of multicellular organisms. At least cadherins 1-13 as well as types B, E, EP, M, N, P and R have been characterized. Among the functions cadherins are known for, with some exceptions, cadherins participate in cell aggregation and are associated with cell-cell adhesion sites. Recently, it has been reported that while all cadherins share multiple repeats of a cadherin specific motif believed to correspond to folding of extracellular domains, members of the cadherin superfamily have divergent structures and, possibly, functions. In particular it has been reported that members of the cadherin superfamily are involved in signal transduction. See, Suzuki, J. Cell Biochem., 61(4):531-542 (1996). Cadherins are further described in Tanihara, et al., J. Cell Sci., 107(6):1697-1704 (1994), Aberle, et al., J. Cell Biochem., 61(4):514-523 (1996) and Tanihara, et al., Cell Adhes. Commun., 2(1):15-26 (1994).

Protocadherins are members of the cadherin superfamily which are highly expressed in the brain. In some studies, protocadherins have shown cell adhesion activity. See, Sano, et al., EMBO J., 12(6):2249-2256 (1993). However, studies have also shown that some protocadherins, such as protocadherin 3 (also referred to as Pcdh3 or pc3), do not show strong calcium dependent cell aggregation activity. See, Sago, et al., Genomics, 29(3):631-640 (1995) for this study and further characteristics of Pcdh3.

Therefore, novel members of the cadherin superfamily are of interest. More generally, all membrane-bound proteins and receptors are of interest. Such proteins can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are therefore being undertaken by both industry and academia to identify new, native membrane bound proteins, particular those having sequence identity with protocadherins, especially 3 and 4. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. Provided herein are the results of such efforts.

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63. **PRO534**

Protein disulfide isomerase is an enzymatic protein which is involved in the promotion of correct refolding of proteins through the establishment of correct disulfide bond formation. Protein disulfide isomerase was initially identified based upon its ability to catalyze the renaturation of reduced denatured RNase (Goldberger et al., *J. Biol. Chem.* 239:1406-1410 (1964) and Epstein et al., *Cold Spring Harbor Symp. Quant. Biol.* 28:439-449 (1963)). Protein disulfide isomerase has been shown to be a resident enzyme of the endoplasmic reticulum which is retained in the endoplasmic reticulum via a -KDEL or -HDEL amino acid sequence at its C-terminus. Protein disulfide isomerase and related proteins are further described in Laboissiere, et al., *J. Biol. Chem.*, 270(47):28006-28009 (1995); Jeenes, et al., *Gene*, 193(2):151-156 (1997); Koivunen, et al., *Genomics*, 42(3):397-404 (1997); and Desilva, et al., *DNA Cell Biol.*, 15(1):9-16 (1996). These studies indicate the importance of the identification of protein disulfide related proteins.

More generally, and also of interest are all novel membrane-bound proteins and receptors. Such proteins can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin

molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Given the importance of membrane bound proteins, efforts are under way to identify novel membrane bound proteins. Moreover, given the importance of disulfide bond-forming enzymes and their potential uses in a number of different applications, for example in increasing the yield of correct refolding of recombinantly produced proteins, efforts are currently being undertaken by both industry and academia to identify new, native proteins having sequence identity with protein disulfide isomerase. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel protein disulfide isomerase homologs. We herein describe a novel polypeptide having sequence identity with protein disulfide isomerase and the nucleic acids encoding the same.

64. PRO697

Secreted frizzled related proteins (sFRPs) are related to the frizzled family of transmembrane receptors. The sFRPs are approximately 30 kDa in size, and each contains a putative signal sequence, a frizzled-like cysteine-rich domain, and a conserved hydrophilic carboxy-terminal domain. It has been reported that sFRPs may function to modulate Wnt signaling, or function as ligands for certain receptors. Rattner, et al., *PNAS USA*, 94(7):2859-2863 (1997). Therefore, sFRPs and proteins having sequence identity and/or similarity to sFRPs are of interest.

Another secreted protein of interest is any member of the family of secreted apoptosis-related proteins (SARPs). Expression of SARPs modifies the intracellular levels of beta-catenin, suggesting that SARPs interfere with the Wnt-frizzled proteins signaling pathway. Melkonyan, et al., *PNAS USA*, 94(25):13636-13641 (1997). Therefore, SARPs and proteins having sequence identity and/or similarity to SARPs are of interest.

In addition to sFRPs and SARPs, many extracellular proteins are of interest. Extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents.

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins, particularly those having sequence identity or similarity with sFRP-2 and SARP-1. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

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65. PRO717

Efforts are being undertaken by both industry and academia to identify new, native transmembrane receptor proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. The results of such efforts are provided herein.

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66. PRO731

Cadherins are a large family of transmembrane proteins. Cadherins comprise a family of calcium-dependent glycoproteins that function in mediating cell-cell adhesion in virtually all solid tissues of multicellular organisms. At least cadherins 1-13 as well as types B, E, EP, M, N, P and R have been characterized. Among the functions 15 cadherins are known for, with some exceptions, cadherins participate in cell aggregation and are associated with cell-cell adhesion sites. Recently, it has been reported that while all cadherins share multiple repeats of a cadherin specific motif believed to correspond to folding of extracellular domains, members of the cadherin superfamily have divergent structures and, possibly, functions. In particular it has been reported that members of the cadherin superfamily are involved in signal transduction. See, Suzuki, J. Cell Biochem., 61(4):531-542 (1996). Cadherins 20 are further described in Tanihara, et al., J. Cell Sci., 107(6):1697-1704 (1994), Aberle, et al., J. Cell Biochem., 61(4):514-523 (1996) and Tanihara, et al., Cell Adhes. Commun., 2(1):15-26 (1994).

Protocadherins are members of the cadherin superfamily which are highly expressed in the brain. In some studies, protocadherins have shown cell adhesion activity. See, Sano, et al., EMBO J., 12(6):2249-2256 (1993). However, studies have also shown that some protocadherins, such as protocadherin 3 (also referred to as Pcdh3 or 25 pc3), do not show strong calcium dependent cell aggregation activity. See, Sago, et al., Genomics, 29(3):631-640 (1995) for this study and further characteristics of Pcdh3.

Therefore, novel members of the cadherin superfamily are of interest. More generally, all membrane-bound 30 proteins and receptors are of interest. Such proteins can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and 35 cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are therefore being undertaken by both industry and academia to identify new, native membrane bound proteins, particular those having sequence identity with protocadherins, especially 4, 68, 43, 42, 3 and 5. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. Provided herein are the results of such efforts.

67. PRO218

Efforts are being undertaken by both industry and academia to identify new, native membrane bound proteins, particularly those having sequence identity with membrane regulator proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins.

15 68. PRO768

The integrins comprise a supergene family of cell-surface glycoprotein receptors that promote cellular adhesion. Each cell has numerous receptors that define its cell adhesive capabilities. Integrins are involved in a wide variety of interaction between cells and other cells or matrix components. The integrins are of particular importance in regulating movement and function of immune system cells. The platelet IIb/IIIa integrin complex is of particular importance in regulating platelet aggregation. A member of the integrin family, integrin β -6, is expressed on epithelial cells and modulates epithelial inflammation. Another integrin, leucocyte-associated antigen-1 (LFA-1) is important in the adhesion of lymphocytes during an immune response.

Of particular interest is H36-alpha 7, an integrin alpha chain that is developmentally regulated during myogenesis as described in Song, et al., *J. Cell Biol.*, 117(3):643-657 (1992). The expression pattern of the laminin-binding alpha 7 beta 1 integrin is developmentally regulated in skeletal, cardiac, and smooth muscle. Ziober, et al., *Mol. Biol. Cell*, 8(9):1723-1734 (1997). It has been reported that expression of the alpha 7-X1/X2 integrin is a novel mechanism that regulates receptor affinity states in a cell-specific context and may modulate integrin-dependent events during muscle development and repair. *Id.* It has further been reported that laminins promote the locomotion of skeletal myoblasts via the alpha 7 integrin receptor. In particular it was reported that alpha 7 beta 1 receptor can promote myoblast adhesion and motility on a restricted number of laminin isoforms and may be important in myogenic precursor recruitment during regeneration and differentiation. Yao, et al., *J. Cell Sci.*, 109(13):3139-3150 (1996). Spliced variants of integrin alpha 7 are also described in Leung, et al., *Biochem. Biophys. Res. Commun.*, 243(1):317-325 (1998) and Fornaro and Languino, *Matrix Biol.*, 16(4):185-193 (1997). Moreover, it has been reported that absence of integrin alpha 7 causes a form of muscular dystrophy. Thus integrins, particularly those related to integrin 7 and related molecules, are of interest.

In addition to the interest of integrins, more generally, all membrane-bound proteins and receptors are of interest since such proteins can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate

environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Therefore, efforts are being undertaken by both industry and academia to identify new, native receptor proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. The results of such efforts, particularly those focused on identifying new polypeptides having sequence identity with integrins, are provided herein.

69. **PRO771**

Testican is a multidomain testicular proteoglycan which is expressed in numerous tissue types including, but not limited to neuromuscular tissue, the brain and reproductive tissues. Testican resembles modulators of cell social behavior such as the regulation of cell shape, adhesion, migration and proliferation. [Bonnet, F. et al., *J. Biol. Chem.*, **271**(8):4373 (1996), Perin, J.P. et al., *EXS* (Switzerland), **70**:191 (1994), Alliel, P.M., et al. *Eur. J. Biochem.*, **214**(1):346 (1993), Charbonnier, F., et al., *C. R. Seances Soc. Biol. Fil.* (France), **191**(1):127 (1997)]. Among other reasons, since testican has been implicated in neuronal processes and may be associated with the growth of connective tissue, testican and related molecules are of interest.

More generally, all extracellular proteins are of interest. Extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad.*

Sci., 23:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts, particularly those focused on identifying molecules having identity and/or similarity with testican are of interest.

70. PRO733

T1/ST2 is a receptor-like molecule homologous to the type I interleukin-1 receptor, believed to be involved 5 in cell signaling. The T1/ST2 receptor and/or putative ligands are further described in Gayle, et al., J. Biol. Chem., 271(10):5784-5789 (1996), Kumar, et al., J. Biol. Chem., 270(46):27905-27913 (1995), and Mitcham, et al., J. Biol. Chem., 271(10):5777-5783 (1996). These proteins, and proteins related thereto are of interest.

More generally all membrane-bound proteins and receptors are of interest since they can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, 10 e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, 15 receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as 20 pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native receptor proteins. Many 25 efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. The results of such efforts are provided herein.

71. PRO162

Pancreatitis-associated protein (PAP) is a secretory protein that is overexpressed by the pancreas during acute pancreatitis. Serum PAP concentrations have been shown to be abnormally high in patients with acute 30 pancreatitis. Pezzilli et al., Am. J. Gastroenterol., 92(10):1887-1890 (1997).

PAP is synthesized by the pancreas due to pancreatic inflammation and has been shown to be a good serum marker for injury of the pancreas. In addition, serum PAP levels appear to strongly correlate with creatinine clearance measurements. In patients with a pancreas-kidney transplantation, PAP may prove to be a useful biological and histological marker of pancreatic graft rejection. Van der Pijl et al., Transplantation, 63(7):995-1003 (1997). 35 Further, PAP has been shown to be useful in screening neonates for cystic fibrosis. In fact, PAP may discriminate cystic fibrosis neonates with better specificity than the current immunoreactive trypsin assay. Iovanna et al., C. R. Acad. Aci. III, 317(6):561-564.

Secreted proteins such as PAP have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons,

interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents.

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts are presented herein.

72. **PRO788**

Anti-neoplastic urinary protein (ANUP) was identified as the major protein present in a fraction of human urine which exhibits antiproliferative activity against human tumor cell lines without affecting the growth of several normal diploid cell lines or tumor cells of mouse or hamster origin. Sloane et al., *Biochem. J.*, 234(2):355-362 (1986).

ANUP is a unique cytokine that has been found in human granulocytes. The N-terminal amino acid sequence has been shown to be unique. A synthetic peptide corresponding to the first nine residues, with Cys at positions 4 and 7, was found to be an anti-tumor agent in vitro. Ridge and Sloane, *Cytokine*, 8(1):1-5 (1996).

Secreted proteins such as ANUP have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

25 73. **PRO1008**

Dickkopf-1 (dkk-1) is a member of a family of secreted proteins and functions in head induction. Dkk-1 is an inducer of Spemann organizer in amphibian embryos. Glinka, et al., *Nature*, 391(6665):357-362 (1998). Dkk-1 is a potent antagonist of Wnt signalling, suggesting that dkk genes encode a family of secreted Wnt inhibitors. Thus, dkk-1 family members and related molecules are of interest.

More generally, all extracellular proteins are of interest since they can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins,

erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents.

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins, particularly those related to dkk-1. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques 5 are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts to identify molecules related to dkk-1 are provided herein.

74. **PRO1012**

Protein disulfide isomerase is an enzymatic protein which is involved in the promotion of correct refolding 10 of proteins through the establishment of correct disulfide bond formation. Protein disulfide isomerase was initially identified based upon its ability to catalyze the renaturation of reduced denatured RNase (Goldberger et al., *J. Biol. Chem.* 239:1406-1410 (1964) and Epstein et al., *Cold Spring Harbor Symp. Quant. Biol.* 28:439-449 (1963)). Protein disulfide isomerase has been shown to be a resident enzyme of the endoplasmic reticulum which is retained 15 in the endoplasmic reticulum via a -KDEL or -HDEL amino acid sequence at its C-terminus. Protein disulfide isomerase and related proteins are further described in Laboissiere, et al., *J. Biol. Chem.*, 270(47):28006-28009 (1995); Jeenes, et al., *Gene*, 193(2):151-156 (1997); Koivunen, et al., *Genomics*, 42(3):397-404 (1997); and Desilva, et al., *DNA Cell Biol.*, 15(1):9-16 (1996). These studies indicate the importance of the identification of protein disulfide related proteins.

More generally, the identification of all extracellular and membrane-bound proteins is of interest since they 20 play important roles in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound 25 proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment, usually at a membrane-bound receptor protein.

Secreted proteins have various industrial applications, including use as pharmaceuticals, diagnostics, biosensors and bioreactors. In fact, most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their 30 receptors, which are membrane-bound proteins, also have potential as therapeutic or diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. Membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and 35 cellular adhesin molecules like selectins and integrins. Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Of particular interest are cellular proteins having endoplasmic reticulum (ER) retention signals. These proteins are retained in the cell and function closely with endoplasmic reticulum in protein production. Such proteins have been described previously, i.e., see Shorosh and Dixon, *Plant J.*, 2(1):51-58 (1992).

Efforts are being undertaken by both industry and academia to identify new, native secreted and membrane-bound receptor proteins, and in particular, cellular proteins having ER retention signals. Many efforts are focused
5 on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S. Patent No. 5,536,637]. The results of such efforts, particularly the identification of novel polypeptides and nucleic acids encoding the same, which have sequence identity and similarity to protein disulfide isomerase are presented herein.

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75. PRO1014

Oxygen free radicals and antioxidants appear to play an important role in the central nervous system after cerebral ischemia and reperfusion. Moreover, cardiac injury, related to ischaemia and reperfusion has been reported to be caused by the action of free radicals. Additionally, studies have reported that the redox state of the cell is a
15 pivotal determinant of the fate of the cells. Furthermore, reactive oxygen species have been reported to be cytotoxic, causing inflammatory disease, including tissue necrosis, organ failure, atherosclerosis, infertility, birth defects, premature aging, mutations and malignancy. Thus, the control of oxidation and reduction is important for a number of reasons including for control and prevention of strokes, heart attacks, oxidative stress and hypertension. In this regard, reductases, and particularly, oxidoreductases, are of interest. Publications further describing this subject
20 matter include Kelsey, et al., *Br. J. Cancer*, 76(7):852-4 (1997); Friedrich and Weiss, *J. Theor. Biol.*, 187(4):529-40 (1997) and Pieulle, et al., *J. Bacteriol.*, 179(18):5684-92 (1997).

In addition to reductases in particular, novel polypeptides are generally of interest. Extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed
25 by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

30 Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening
35 of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S. Patent No. 5,536,637]. The results of such efforts, particularly those identifying polypeptides having sequence identity with reductases, and the nucleic acids encoding the same, are presented herein.

76. PRO1017

Enzymatic proteins play important roles in the chemical reactions involved in the digestion of foods, the biosynthesis of macromolecules, the controlled release and utilization of chemical energy, and other processes necessary to sustain life. Sulfotransferases are enzymes which transfer sulfate from a sulfate donor to acceptor substrates, particularly those containing terminal glucuronic acid. The HNK-1 carbohydrate epitope is expressed 5 on several neural adhesion glycoproteins and a glycolipid, and is involved in cell interactions. The glucuronyltransferase and sulfotransferase are considered to be the key enzymes in the biosynthesis of this epitope because the rest of the structure occurs often in glycoconjugates. HNK-1 sulfotransferase is further described in Bakker, H., et al., *J. Biol. Chem.*, 272(47):29942-29946 (1997).

In addition to HNK-1 sulfotransferase, and novel proteins related thereto, all novel proteins are of 10 interest. Extracellular and membrane-bound proteins play important roles in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, 15 received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment, usually at a membrane-bound receptor protein.

Secreted proteins have various industrial applications, including use as pharmaceuticals, diagnostics, biosensors and bioreactors. In fact, most protein drugs available at present, such as thrombolytic agents, interferons, 20 interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane-bound proteins, also have potential as therapeutic or diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. Membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of 25 the relevant receptor/ligand interaction. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Efforts are being undertaken by both industry and academia to identify new, native secreted and membrane-bound receptor proteins, particularly those having sequence identity with HNK-1 sulfotransferase. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S. Patent No. 35 5,536,637)]. The results of such efforts are provided herein.

77. PRO474

Enzymatic proteins play important roles in the chemical reactions involved in the digestion of foods, the biosynthesis of macromolecules, the controlled release and utilization of chemical energy, and other processes

necessary to sustain life. Glucose dehydrogenase functions in the oxidation of glucose to gluconate to generate metabolically useful energy. The regulation of the PQQ-linked glucose dehydrogenase in different organisms is reviewed in Neijssel, et al., *Antonie Van Leeuwenhoek*, 56(1):51-61 (1989). Glucose dehydrogenase functions as an auxiliary energy generating mechanism, because it is maximally synthesized under conditions of energy stress.

In addition to molecules related to glucose dehydrogenase, all novel proteins are of interest. Extracellular and membrane-bound proteins play important roles in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment, usually at a membrane-bound receptor protein.

Secreted proteins have various industrial applications, including use as pharmaceuticals, diagnostics, biosensors and bioreactors. In fact, most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane-bound proteins, also have potential as therapeutic or diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. Membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Efforts are being undertaken by both industry and academia to identify new, native secreted and membrane-bound receptor proteins, and particularly cellular proteins and those related to dehydrogenase or oxidoreductase. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S. Patent No. 5,536,637]. The results of such efforts are presented herein.

78. PRO1031

It has been reported that the cytokine interleukin 17 (IL-17) stimulates epithelial, endothelial, and fibroblastic cells to secrete cytokines such as IL-6, IL-8, and granulocyte-colony-stimulating factor, as well as prostaglandin E2. Moreover, it has been shown that when cultured in the presence of IL-17, fibroblasts could sustain proliferation of CD34+ preferential maturation into neutrophils. Thus it has been suggested that IL-17 constitutes an early initiator of the T cell-dependent inflammatory reaction and/or an element of the cytokine network that bridges the immune system to hematopoiesis. See, Yao, et al., *J. Immunol.*, 155(12):5483-5486 (1995); Fossiez, et al., *J. Exp. Med.*, 183(6):2593-2603 (1996); Kennedy, et al., *J. Interferon Cytokine Res.*, 16(8):611-617 (1996). Thus, proteins related

to IL-17 are of interest.

More generally, all novel proteins are of interest. Extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides 5 (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors 10 and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents.

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins, particularly those related to IL-17. Many efforts are focused on the screening of mammalian recombinant DNA 15 libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, **93**:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts are presented herein.

79. PRO938

20 Protein disulfide isomerase is an enzymatic protein which is involved in the promotion of correct refolding of proteins through the establishment of correct disulfide bond formation. Protein disulfide isomerase was initially identified based upon its ability to catalyze the renaturation of reduced denatured RNase (Goldberger et al., *J. Biol. Chem.* **239**:1406-1410 (1964) and Epstein et al., *Cold Spring Harbor Symp. Quant. Biol.* **28**:439-449 (1963)). Protein disulfide isomerase has been shown to be a resident enzyme of the endoplasmic reticulum which is retained 25 in the endoplasmic reticulum via a -KDEL or -HDEL amino acid sequence at its C-terminus. Protein disulfide isomerase and related proteins are further described in Laboissiere, et al., *J. Biol. Chem.*, **270**(47):28006-28009 (1995); Jeenes, et al., *Gene*, **193**(2):151-156 (1997); Koivunen, et al., *Genomics*, **42**(3):397-404 (1997); Desilva, et al., *DNA Cell Biol.*, **15**(1):9-16 (1996); Freedman, et al. *Trends in Biochem. Sci.* **19**:331-336 (1994); Bulleid, N.J. *Advances in Prot. Chem.* **44**:125-50 (1993); and Noiva, R., *Prot. Exp. and Purification* **5**:1-13 (1994). These studies 30 indicate the importance of the identification of protein disulfide related proteins.

More generally, and also of interest are all novel membrane-bound proteins and receptors. Such proteins can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often 35 transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and

differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents 5 to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Given the importance of membrane bound proteins, efforts are under way to identify novel membrane bound proteins. Moreover, given the importance of disulfide bond-forming enzymes and their potential uses in a number of different applications, for example in increasing the yield of correct refolding of recombinantly produced proteins, 10 efforts are currently being undertaken by both industry and academia to identify new, native proteins having sequence identity with protein disulfide isomerase. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel protein disulfide isomerase homologs.

We herein describe the identification and characterization of a novel polypeptide having homology to protein disulfide isomerase.

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80. PRO1082

The low density lipoprotein (LDL) receptor is a membrane-bound protein that plays a key role in cholesterol homeostasis, mediating cellular uptake of lipoprotein particles by high affinity binding to its ligands, apolipoprotein (apo) B-100 and apoE. The ligand-binding domain of the LDL receptor contains 7 cysteine-rich repeats of 20 approximately 40 amino acids, wherein each repeat contains 6 cysteines, which form 3 intra-repeat disulfide bonds.

These unique structural features provide the LDL receptor with its ability to specifically interact with apo B-100 and apoE, thereby allowing for transport of these lipoprotein particles across cellular membranes and metabolism of their components. Soluble fragments containing the extracellular domain of the LDL receptor have been shown to retain the ability to interact with its specific lipoprotein ligands (Simmons et al., *J. Biol. Chem.* 272:25531-25536 (1997)). 25 LDL receptors are further described in Javitt, *FASEB J.*, 9(13):1378-1381 (1995) and Herz and Willnow, *Ann. NY Acad. Sci.*, 737:14-19 (1994). Thus, proteins having sequence identity with LDL receptors are of interest.

More generally, all membrane-bound proteins and receptors can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other 30 cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, 35 transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor. Of particular interest are membrane bound proteins that have type II transmembrane domains.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are thus being undertaken by both industry and academia to identify new, native proteins, particularly 5 membrane bound proteins including type II transmembrane bound proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. The results of such efforts are provided herein.

81. PRO1083

10 Of particular interest are membrane bound proteins that belong to the seven transmembrane (7TM) receptor superfamily. Examples of these receptors include G-protein coupled receptors such as ion receptors. Another example of a 7TM receptor superfamily member is described in Osterhoff, et al., *DNA Cell Biol.*, 16(4):379-389 (1997).

15 Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native receptor proteins. Many 20 efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. The results of such efforts are presented herein.

82. PRO200

25 Polypeptides involved in survival, proliferation and/or differentiation of cells are of interest. Polypeptides known to be involved in the survival, proliferation and/or differentiation of cells include VEGF and members of the bone morphogenetic protein family. Therefore, novel polypeptides which are related to either VEGF or the bone morphogenetic protein are of interest.

The heparin-binding endothelial cell-growth factor, VEGF, was identified and purified from media conditioned by bovine pituitary follicular or folliculo-stellate cells over several years ago. See Ferrara et al., *Biophys. Res. Comm.* 161, 851 (1989). VEGF is a naturally occurring compound that is produced in follicular or 30 folliculo-stellate cells (FC), a morphologically well characterized population of granular cells. The FC are stellate cells that send cytoplasmic processes between secretory cells.

VEGF is expressed in a variety of tissues as multiple homodimeric forms (121, 165, 189 and 206 amino acids per monomer) resulting from alternative RNA splicing. VEGF₁₂₁ is a soluble mitogen that does not bind heparin; the longer forms of VEGF bind heparin with progressively higher affinity. The heparin-binding forms of 35 VEGF can be cleaved in the carboxy terminus by plasmin to release (a) diffusible form(s) of VEGF. Amino acid sequencing of the carboxy terminal peptide identified after plasmin cleavage is Arg₁₁₀-Ala₁₁₁. Amino terminal "core" protein, VEGF (1-110) isolated as a homodimer, binds neutralizing monoclonal antibodies (4.6.1 and 2E3) and soluble forms of FMS-like tyrosine kinase (FLT-1), kinase domain region (KDR) and fetal liver kinase (FLK) receptors with similar affinity compared to the intact VEGF₁₆₅ homodimer.

As noted, VEGF contains two domains that are responsible respectively for binding to the KDR and FLT-1 receptors. These receptors exist only on endothelial (vascular) cells. As cells become depleted in oxygen, because of trauma and the like, VEGF production increases in such cells which then bind to the respective receptors in order to signal ultimate biological effect. The signal then increases vascular permeability and the cells divide and expand to form new vascular pathways - vasculogenesis and angiogenesis.

5 Thus, VEGF is useful for treating conditions in which a selected action on the vascular endothelial cells, in the absence of excessive tissue growth, is important, for example, diabetic ulcers and vascular injuries resulting from trauma such as subcutaneous wounds. Being a vascular (artery and venus) endothelial cell growth factor, VEGF restores cells that are damaged, a process referred to as vasculogenesis, and stimulates the formulation of new vessels, a process referred to as angiogenesis.

10 VEGF would also find use in the restoration of vasculature after a myocardial infarct, as well as other uses that can be deduced. In this regard, inhibitors of VEGF are sometimes desirable, particularly to mitigate processes such as angiogenesis and vasculogenesis in cancerous cells.

15 Regarding the bone morphogenetic protein family, members of this family have been reported as being involved in the differentiation of cartilage and the promotion of vascularization and osteoinduction in preformed hydroxyapatite. Zou, et al., *Genes Dev.* (U.S.), 11(17):2191 (1997); Levine, et al., *Ann. Plast. Surg.*, 39(2):158 (1997). A number of related bone morphogenetic proteins have been identified, all members of the bone morphogenetic protein (BMP) family. Bone morphogenetic native and mutant proteins, nucleic acids encoding therefor, related compounds including receptors, host cells and uses are further described in at least: U.S. Patent Nos. 5,670,338; 5,454,419; 5,661,007; 5,637,480; 5,631,142; 5,166,058; 5,620,867; 5,543,394; 4,877,864; 5,013,649; 20 55,106,748; and 5,399,677. Of particular interest are proteins having homology with bone morphogenetic protein 1, a procollagen C-proteinase that plays key roles in regulating matrix deposition.

25 The present invention is predicated upon research intended to identify novel polypeptides which are related to VEGF and the BMP family, and in particular, polypeptides which have a role in the survival, proliferation and/or differentiation of cells. While the novel polypeptides are not expected to have biological activity identical to the known polypeptides to which they have homology, the known polypeptide biological activities can be used to determine the relative biological activities of the novel polypeptides. In particular, the novel polypeptides described herein can be used in assays which are intended to determine the ability of a polypeptide to induce survival, proliferation or differentiation of cells. In turn, the results of these assays can be used accordingly, for diagnostic and therapeutic purposes. The results of such research is the subject of the present invention.

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83. PRO285 and PRO286

The cloning of the Toll gene of *Drosophila*, a maternal effect gene that plays a central role in the establishment of the embryonic dorsal-ventral pattern, has been reported by Hashimoto *et al.*, *Cell* 52, 269-279 (1988). The *Drosophila* Toll gene encodes an integral membrane protein with an extracytoplasmic domain of 803 amino acids and a cytoplasmic domain of 269 amino acids. The extracytoplasmic domain has a potential membrane-spanning segment, and contains multiple copies of a leucine-rich segment, a structural motif found in many transmembrane proteins. The Toll protein controls dorsal-ventral patterning in *Drosophila* embryos and activates the transcription factor Dorsal upon binding to its ligand Spätzle. (Morisato and Anderson, *Cell* 76, 677-688 (1994).) In adult *Drosophila*, the Toll/Dorsal signaling pathway participates in the anti-fungal immune response. (Lenainre et

al., *Cell* 86, 973-983 (1996).)

A human homologue of the *Drosophila* Toll protein has been described by Medzhitov et al., *Nature* 388, 394-397 (1997). This human Toll, just as *Drosophila* Toll, is a type I transmembrane protein, with an extracellular domain consisting of 21 tandemly repeated leucine-rich motifs (leucine-rich region - LRR), separated by a non-LRR region, and a cytoplasmic domain homologous to the cytoplasmic domain of the human interleukin-1 (IL-1) receptor.

5 A constitutively active mutant of the human Toll transfected into human cell lines was shown to be able to induce the activation of NF- κ B and the expression of NF- κ B-controlled genes for the inflammatory cytokines IL-1, IL-6 and IL-8, as well as the expression of the constitulatory molecule B7.1, which is required for the activation of native T cells. It has been suggested that Toll functions in vertebrates as a non-clonal receptor of the immune system, which can induce signals for activating both an innate and an adaptive immune response in vertebrates. The human Toll

10 gene reported by Medzhitov et al., *supra* was most strongly expressed in spleen and peripheral blood leukocytes (PBL), and the authors suggested that its expression in other tissues may be due to the presence of macrophages and dendritic cells, in which it could act as an early-warning system for infection. The public GenBank database contains the following Toll sequences: Toll1 (DNAX# HSU88540-1, which is identical with the random sequenced full-length cDNA #HUMRSC786-1); Toll2 (DNAX# HSU88878-1); Toll3 (DNAX# HSU88879-1); and Toll4 (DNAX#

15 HSU88880-1, which is identical with the DNA sequence reported by Medzhitov et al., *supra*). A partial Toll sequence (Toll5) is available from GenBank under DNAX# HSU88881-1.

Further human homologues of the *Drosophila* Toll protein, designated as Toll-like receptors (huTLRs1-5) were recently cloned and shown to mirror the topographic structure of the *Drosophila* counterpart (Rock et al., *Proc. Natl. Acad. Sci. USA* 95, 588-593 [1998]). Overexpression of a constitutively active mutant of one human TLR

20 (Toll-protein homologue - Medzhitov et al., *supra*; TLR4 - Rock et al., *supra*) leads to the activation of NF- κ B and induction of the inflammatory cytokines and constitulatory molecules. Medzhitov et al., *supra*.

84. PRO213-1, PRO1330 and PRO1449

Cancer is characterized by the increase in the number of abnormal, or neoplastic, cells derived from a

25 normal tissue which proliferate to form a tumor mass, the invasion of adjacent tissues by these neoplastic tumor cells, and the generation of malignant cells which eventually spread via the blood or lymphatic system to regional lymph nodes and to distant sites (metastasis). In a cancerous state a cell proliferates under conditions in which normal cells would not grow. Cancer manifests itself in a wide variety of forms, characterized by different degrees of invasiveness and aggressiveness.

30 Alteration of gene expression is intimately related to the uncontrolled cell growth and de-differentiation which are a common feature of all cancers. The genomes of certain well studied tumors have been found to show decreased expression of recessive genes, usually referred to as tumor suppression genes, which would normally function to prevent malignant cell growth, and/or overexpression of certain dominant genes, such as oncogenes, that act to promote malignant growth. Each of these genetic changes appears to be responsible for importing some of the

35 traits that, in aggregate, represent the full neoplastic phenotype (Hunter, *Cell* 64, 1129 [1991]; Bishop, *Cell* 64, 235-248 [1991]).

A well known mechanism of gene (e.g. oncogene) overexpression in cancer cells is gene amplification. This is a process where in the chromosome of the ancestral cell multiple copies of a particular gene are produced. The process involves unscheduled replication of the region of chromosome comprising the gene, followed by

recombination of the replicated segments back into the chromosome (Alitalo et al., *Adv. Cancer Res.* 47, 235-281 [1986]). It is believed that the overexpression of the gene parallels gene amplification, i.e. is proportionate to the number of copies made.

Proto-oncogenes that encode growth factors and growth factor receptors have been identified to play important roles in the pathogenesis of various human malignancies, including breast cancer. For example, it has been 5 found that the human ErbB2 gene (*erbB2*, also known as *her2*, or *c-erbB-2*), which encodes a 185-kd transmembrane glycoprotein receptor (*p185HER2; HER2*) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer (Slamon et al., *Science* 235:177-182 [1987]; Slamon et al., *Science* 244:707-712 [1989]).

It has been reported that gene amplification of a protooncogene is an event typically involved in the more 10 malignant forms of cancer, and could act as a predictor of clinical outcome (Schwab et al., *Genes Chromosomes Cancer* 1, 181-193 [1990]; Alitalo et al., *supra*). Thus, *erbB2* overexpression is commonly regarded as a predictor of a poor prognosis, especially in patients with primary disease that involves axillary lymph nodes (Slamon et al., [1987] and [1989], *supra*; Ravdin and Chamness, *Gene* 159:19-27 [1995]; and Hynes and Stern, *Biochem Biophys Acta* 1198: 165-184 [1994]), and has been linked to sensitivity and/or resistance to hormone therapy and 15 chemotherapeutic regimens, including CMF (cyclophosphamide, methotrexate, and fluorouracil) and anthracyclines (Baselga et al., *Oncology* 11 (3 Suppl 1): 43-48 [1997]). However, despite the association of *erbB2* overexpression with poor prognosis, the odds of HER2-positive patients responding clinically to treatment with taxanes were greater than three times those of HER2-negative patients (*Ibid*). A recombinant humanized anti-ErbB2 (anti-HER2) 20 monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, referred to as rhuMAb HER2 or Herceptin 78) has been clinically active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anticancer therapy. (Baselga et al., *J. Clin. Oncol.* 14:737-744 [1996]).

The protein Notch and its homologues are key regulatory receptors in determining the cell fate in various development processes. The protein Notch-4, also known as int-3 oncogene, was originally identified as a frequent 25 target in mouse mammary tumor virus (MMVS). Notch-4 is believed to be a transgene which affects the differentiation capacity of stem cells and leads to neoplastic proliferation in epithelial cells. Shirayoshi et al., *Genes Cells* 2(3): 213-224 (1997). During embryogenesis, the expression of Notch-4 was detected in endothelial cells of blood vessels forming tissues such as the dorsal aorta, intersegmental vessels, yolk sac vessels, cephalic vessels, heart, vessels in branchial arches, and capillary plexuses. Notch-4 expression in these tissues was also associated 30 with *fik-1*, the major regulatory gene of vasculogenesis and angiogenesis. Notch-4 is also upregulated *in vitro* during the differentiation of endothelial stem cell. The endothelial cell specific expression pattern of Notch-4, as well as its structural similarity to Notch suggest that Notch-4 is an endothelial cell specific homologue of Notch and that it may play a role in vasculogenesis and angiogenesis.

85. **PRO298**

Efforts are being undertaken by both industry and academia to identify new, native receptor proteins. Many 35 efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO298 polypeptides.

86. **PRO337**

Neuronal development in higher vertebrates is characterized by processes that must successfully navigate distinct cellular environment en route to their synaptic targets. The result is a functionally precise formation of neural circuits. The precision is believed to result from mechanisms that regulate growth cone pathfinding and target recognition, followed by latter refinement and remodeling of such projections by events that require neuronal activity,

- 5 Goodman and Shatz, *Cell/Neuron* [Suppl.] 72(10): 77-98 (1993). It is further evident that different neurons extend nerve fibers that are biochemically distinct and rely on specific guidance cues provided by cell-cell, cell-matrix, and chemotropic interactions to reach their appropriate synaptic targets, Goodman et al., *supra*.

One particular means by which diversity of the neuronal cell surface may be generated is through differential expression of cell surface proteins referred to as cell adhesion molecules (CAMs). Neuronally expressed CAMs have
10 been implicated in diverse developmental processes, including migration of neurons along radial glial cells, providing permissive or repulsive substrates for neurite extension, and in promoting the selective fasciculation of axons in projectional pathways. Jessel, *Neuron* 1: 3-13 (1988); Edelman and Crossin, *Annu. Rev. Biochem.* 60: 155-190 (1991). Interactions between CAMs present on the growth cone membrane and molecules on opposing cell membranes or in the extracellular matrix are thought to provide the specific guidance cues that direct nerve fiber
15 outgrowth along appropriate projectional pathways. Such interactions are likely to result in the activation of various second messenger systems within the growth cone that regulate neurite outgrowth. Doherty and Walsh, *Curr. Opin Neurobiol.* 2: 595-601 (1992).

In higher vertebrates, most neural CAMs have been found to be members of three major structural families of proteins: the integrins, the cadherins, and the immunoglobulin gene superfamily (IgSF). Jessel, *supra*; Takeichi,
20 *Annu. Rev. Biochem.* 59: 237-252 (1990); Reichardt and Tomaselli, *Annu. Rev. Neurosci.* 14: 531-570 (1991). Cell adhesion molecules of the IgSF (or Ig-CAMs), in particular, constitute a large family of proteins frequently implicated in neural cell interactions and nerve fiber outgrowth during development, Salzer and Colman, *Dev. Neurosci.* 11: 377-390 (1989); Brümmendorf and Rathjen, *J. Neurochem.* 61: 1207-1219 (1993). However, the majority of mammalian Ig-CAMs appear to be too widely expressed to specify navigational pathways or synaptic targets
25 suggesting that other CAMs, yet to be identified, have role in these more selective interactions of neurons.

Many of the known neural Ig-CAMs have been found to be attached to the plasma membrane via a glycosylphosphatidylinositol (GPI) anchor. Additionally, many studies have implicated GPI-anchored proteins in providing specific guidance cues during the outgrowth of neurons in specific pathways. In studies of the grasshopper nervous system, treatment of embryos with phosphatidylinositol-specific phospholipase C (PIPLC), which selectively
30 removes GPI-anchored proteins from the surfaces of cells, resulted in misdirection and faulty navigation among subsets of pioneering growth cones, as well as inhibited migratory patterns of a subset of early neurons, Chang et al., *Devel.* 114: 507-519 (1992). The projection of retinal fibers to the optic tectum appears to depend, in part, on a 33 kDa GPI-anchored protein, however, the precise nature of this protein is unknown. Stahl et al., *Neuron* 5: 735-743 (1990).

35 The expression of various GPI-anchored proteins has been characterized amongst the different populations of primary rat neurons amongst dorsal root ganglion, sympathetic neurons of the cervical ganglion, sympathetic neurons of the superior cervical ganglion, and cerebellar granule neurons. Rosen et al., *J. Cell Biol.* 117: 617-627 (1992). In contrast to the similar pattern of total membrane protein expression by these different types of neurons, striking differences were observed in the expression of GPI-anchored proteins between these neurons. Recently, a

65 kDa protein band known as neurotrimin was discovered and found to be differentially expressed by primary neurons (Rosen et al., *supra*), and restricted to the nervous system and found to be the most abundant and earliest expressed of the GPI-anchored species in the CNS. Struyk et al., *J. Neuroscience* 15(3): 2141-2156 (1995). The discovery of neurotrimin has further lead to the identification of a family of IgSF members, each containing three Ig-like domains that share significant amino acid identity, now termed IgLON. Struyk et al., *supra*; Pimenta et al., *Gene* 170(2): 189-95 (1996).

5 Additional members of the IgLON subfamily include opiate binding cell adhesion molecule (OBCAM), Schofield et al., *EMBO J.* 8: 489-495 (1989); limbic associated membrane protein (LAMP), Pimenta et al., *supra*; CEPU-1; GP55, Wilson et al., *J. Cell Sci.* 109: 3129-3138 (1996); *Eur. J. Neurosci.* 9(2): 334-41 (1997); and AvGp50, Hancox et al., *Brain Res. Mol. Brain Res.* 44(2): 273-85 (1997).

10 While the expression of neurotrimin appears to be widespread, it does appear to correlate with the development of several neural circuits. For example, between E18 and P10, neurotrimin mRNA expression within the forebrain is maintained at high levels in neurons of the developing thalamus, cortical subplate, and cortex, particularly laminae V and VI (with less intense expression in II, III, and IV, and minimal expression in lamina I). Cortical subplate neurons may provide an early, temporary scaffold for the ingrowing thalamic afferents en route to
15 their final synaptic targets in the cortex. Allendoerfer and Shatz, *Annu. Rev. Neurosci.* 17: 185-218 (1994). Conversely, subplate neurons have been suggested to be required for cortical neurons from layer V to select VI to grow into the thalamus, and neurons from layer V to select their targets in the colliculus, pons, and spinal cord (McConnell et al., *J. Neurosci.* 14: 1892-1907 (1994)). The high level expression of neurotrimin in many of these projections suggests that it could be involved in their development.

20 In the hindbrain, high levels of neurotrimin message expression were observed within the pontine nucleus and by the internal granule cells and Purkinje cells of the cerebellum. The pontine nucleus received afferent input from a variety of sources including corticopontine fibers of layer V, and is a major source of afferent input, via mossy fibers, to the granule cells which, in turn, are a major source of afferent input via parallel fibers to Purkinje cells. [Palay and Chan-Palay, *The cerebellar cortex: cytology and organization*. New York: Springer (1974)]. High level
25 expression of neurotrimin in these neurons again suggests potential involvement in the establishment of these circuits.

Neurotrimin also exhibits a graded expression pattern in the early postnatal striatum. Increased neurotrimin expression is found overlying the dorsolateral striatum of the rat, while lesser hybridization intensity is seen overlying the ventromedial striatum. Struyk et al., *supra*. This region of higher neurotrimin hybridization intensity does not correspond to a cytoarchitecturally differentiable region, rather it corresponds to the primary area of afferent input
30 from layer VI of the contralateral sensorimotor cortex (Gerfen, *Nature* 311: 461-464 (1984); Donoghue and Herkenham, *Brain Res.* 365: 397-403 (1986)). The ventromedial striatum, by contrast, receives the majority of its afferent input from the perirhinal and association cortex. It is noteworthy that a complementary graded pattern of LAMP expression, has been observed within the striatum, with highest expression in ventromedial regions, and lowest expression dorsolaterally. Levitt, *Science* 223: 299-301 (1985); Chesselet et al., *Neuroscience* 40: 725-733
35 (1991).

87. **PRO403**

Type II transmembrane proteins, also known as single pass transmembrane proteins have an N-terminal portion lodged in the cytoplasm while the C-terminal portion is exposed to the extracellular domain.

Endothelin is a family of vasoconstrictor peptides about which much activity has been focused to better understand its basic pharmacological, biochemical and molecular biological features, including the presence and structure of isopeptides and their genes (endothelin-1, -2 and β 3), regulation of gene expression, intracellular processing, specific endothelin converting enzymes (ECE), receptor subtypes (ET-A and ET-B), intracellular signal transduction following receptor activation, etc.

5 The endothelin (ET) family of peptides have potent vascular, cardiac and renal actions which may be of pathophysiological importance in many human disease states. ET-1 is expressed as an inactive 212 amino acid prepropeptide. The prepropeptide is first cleaved at Arg52-Cys53 and Arg92-Ala93 and then the carboxy terminal Lys91 and Arg92 are trimmed from the protein to generate the propeptide big ET-1.

10 Endothelin is generated from inactive intermediates, the big endothelins, by a unique processing event catalyzed by the zinc metalloprotease, endothelin converting enzyme (ECE). ECE was recently cloned, and its structure was shown to be a single pass transmembrane protein with a short intracellular N-terminal and a long extracellular C-terminal that contains the catalytic domain and numerous N-glycosylation sites. ECEs cleave the endothelin propeptide between Trp73 and Val74 producing the active peptide, ET, which appears to function as a local rather than a circulating hormone (Rubanyi, G.M. & Polokoff, M.A., *Pharmacological Reviews* 46: 325-415 15 (1994)). Thus ECE activity is a potential site of regulation of endothelin production and a possible target for therapeutic intervention in the endothelin system. By blocking ECE activity, it is possible stop the production of ET-1 by inhibiting the conversion of the relatively inactive precursor, big ET-1, to the physiologically active form.

15 Endothelins may play roles in the pathophysiology of a number of disease states including: 1) cardiovascular diseases (vasospasm, hypertension, myocardial ischemia; reperfusion injury and acute myochardial infarction, stroke (cerebral ischemia), congestive heart failure, shock, atherosclerosis, vascular thickening); 2) kidney disease (acute and chronic renal failure, glomerulonephritis, cirrhosis); 3) lung disease (bronchial asthma, pulmonary hypertension); 4) gastrointestinal disorders (gastric ulcer, inflammatory bowel diseases); 5) reproductive disorders (premature labor, dysmenorrhea, preeclampsia) and 6) carcinogenesis. Rubanyi & Polokoff, *supra*.

25

SUMMARY OF THE INVENTION

1. PRO213

Applicants have identified a cDNA clone that encodes a novel polypeptide, wherein the polypeptide is designated in the present application as "PRO213".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a 30 PRO213 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO213 polypeptide having amino acid residues 1 to 295 of Figure 2 (SEQ ID NO:2), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions.

In another embodiment, the invention provides isolated PRO213 polypeptide. In particular, the invention provides isolated native sequence PRO213 polypeptide, which in one embodiment, includes an amino acid sequence 35 comprising residues 1 to 295 of Figure 2 (SEQ ID NO:2).

2. **PRO274**

Applicants have identified a cDNA clone that encodes a novel polypeptide, wherein the polypeptide is designated in the present application as "PRO274".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO274 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO274 polypeptide having amino acid residues 1 to 492 of Figure 4 (SEQ ID NO:7), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA39987-1184 vector deposited on April 21, 1998 as ATCC 209786 which includes the nucleotide sequence encoding PRO274.

In another embodiment, the invention provides isolated PRO274 polypeptide. In particular, the invention provides isolated native sequence PRO274 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 492 of Figure 4 (SEQ ID NO:7). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO274 polypeptide. Optionally, the PRO274 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA39987-1184 vector deposited on April 21, 1998 as ATCC 209786.

15 In another embodiment, the invention provides three expressed sequence tags (EST) comprising the nucleotide sequences of SEQ ID NO:8 (herein designated as DNA17873), SEQ ID NO:9 (herein designated as DNA36157) and SEQ ID NO:10 (herein designated as DNA28929) (see Figure 5-7, respectively).

3. **PRO300**

20 Applicants have identified a cDNA clone that encodes a novel polypeptide, wherein the polypeptide is designated in the present application as "PRO300".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO300 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO300 polypeptide having amino acid residues 1 to 457 of Figure 9 (SEQ ID NO:19), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA40625-1189 vector deposited on April 21, 1998 as ATCC 209788 which includes the nucleotide sequence encoding PRO300.

30 In another embodiment, the invention provides isolated PRO300 polypeptide. In particular, the invention provides isolated native sequence PRO300 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 457 of Figure 9 (SEQ ID NO:19). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO300 polypeptide. Optionally, the PRO300 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA40625-1189 vector deposited on April 21, 1998 as ATCC 209788.

35 4. **PRO284**

Applicants have identified a cDNA clone that encodes a novel transmembrane polypeptide, wherein the polypeptide is designated in the present application as "PRO284".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO284 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO284 polypeptide

having amino acid residues 1 to 285 of Figure 11 (SEQ ID NO:28), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO284 polypeptide having amino acid residues about 25 to 285 of Figure 11 (SEQ ID NO:28) or 1 or about 25 to X of Figure 11 (SEQ ID NO:28), where X is any amino acid from 71 to 80 of Figure 11 (SEQ ID NO:28), or is complementary to such 5 encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA23318-1211 vector deposited on April 21, 1998 as ATCC 209787 which includes the nucleotide sequence encoding PRO284.

In another embodiment, the invention provides isolated PRO284 polypeptide. In particular, the invention provides isolated native sequence PRO284 polypeptide, which in one embodiment, includes an amino acid sequence 10 comprising residues 1 to 285 of Figure 11 (SEQ ID NO:28). Additional embodiments of the present invention are directed to isolated PRO284 polypeptides comprising amino acids about 25 to 285 of Figure 11 (SEQ ID NO:28) or 1 or about 25 to X of Figure 11 (SEQ ID NO:28), where X is any amino acid from 71 to 80 of Figure 11 (SEQ ID NO:28). Optionally, the PRO284 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA23318-1211 vector deposited on April 21, 1998 as ATCC 209787.

15 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA12982 which comprises the nucleotide sequence of SEQ ID NO:29.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA15886 which comprises the nucleotide sequence of SEQ ID NO:30.

20 5. PRO296

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the sarcoma-amplified protein SAS, wherein the polypeptide is designated in the present application as "PRO296".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO296 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO296 polypeptide 25 having amino acid residues 1 to 204 of Figure 15 (SEQ ID NO:36), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO296 polypeptide having amino acid residues about 35 to 204 of Figure 15 (SEQ ID NO:36) or amino acid 1 or about 35 to X of Figure 15 (SEQ ID NO:36), where X is any amino acid from 42 to 51 of Figure 15 (SEQ ID NO:36), or is complementary to 30 such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA39979-1213 vector deposited on April 21, 1998 as ATCC 209789 which includes the nucleotide sequence encoding PRO296.

In another embodiment, the invention provides isolated PRO296 polypeptide. In particular, the invention provides isolated native sequence PRO296 polypeptide, which in one embodiment, includes an amino acid sequence 35 comprising residues 1 to 204 of Figure 15 (SEQ ID NO:36). Additional embodiments of the present invention are directed to PRO296 polypeptides comprising amino acids about 35 to 204 of Figure 15 (SEQ ID NO:36) or amino acid 1 or about 35 to X of Figure 15 (SEQ ID NO:36), where X is any amino acid from 42 to 51 of Figure 15 (SEQ ID NO:36). Optionally, the PRO296 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA39979-1213 vector deposited on April 21, 1998 as ATCC 209789.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA23020 comprising the nucleotide sequence of SEQ ID NO:37.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA21971 comprising the nucleotide sequence of SEQ ID NO:38.

5 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA29037 comprising the nucleotide sequence of SEQ ID NO:39.

6. **PRO329**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to a high affinity immunoglobulin F_c receptor, wherein the polypeptide is designated in the present application as "PRO329".

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO329 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO329 polypeptide having amino acid residues 1 to 359 of Figure 20 (SEQ ID NO:45), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA40594-1233 vector deposited on February 5, 1998 as ATCC 209617 which includes the nucleotide sequence encoding PRO329.

15 In another embodiment, the invention provides isolated PRO329 polypeptide. In particular, the invention provides isolated native sequence PRO329 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 359 of Figure 20 (SEQ ID NO:45). Optionally, the PRO329 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA40594-1233 vector deposited on February 5, 1998 as ATCC 209617.

7. **PRO362**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to A33 antigen and HCAB membrane-bound protein, wherein the polypeptide is designated in the present application as "PRO362".

20 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO362 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO362 polypeptide having amino acid residues 1 to 321 of Figure 22 (SEQ ID NO:52), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO362 polypeptide having amino acid residues 1 to X of Figure 22 (SEQ ID NO:52) where X is any amino acid from amino acid 271 to 280, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA45416-1251 vector deposited on February 5, 1998 as ATCC 209620 which includes the nucleotide sequence encoding PRO362.

35 In another embodiment, the invention provides isolated PRO362 polypeptide. In particular, the invention provides isolated native sequence PRO362 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 321 of Figure 22 (SEQ ID NO:52). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO362 polypeptide comprising amino acids 1 to X of the amino acid sequence shown in Figure 22 (SEQ ID NO:52), wherein X is any amino acid from amino acid 271 to 280.

Optionally, the PRO362 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA45416-1251 vector deposited on February 5, 1998 as ATCC 209620.

8. **PRO363**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the cell surface receptor protein HCAR, wherein the polypeptide is designated in the present application as "PRO363".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO363 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO363 polypeptide having amino acid residues 1 to 373 of Figure 24 (SEQ ID NO:59), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding a PRO363 extracellular domain polypeptide having amino acid residues 1 to X of Figure 24 (SEQ ID NO:59) where X is any amino acid from amino acid 216 to amino acid 225, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA45419-1252 vector deposited on February 5, 1998 as ATCC 209616 which includes the nucleotide sequence encoding PRO363.

In another embodiment, the invention provides isolated PRO363 polypeptide. In particular, the invention provides isolated native sequence PRO363 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 373 of Figure 24 (SEQ ID NO:59). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO363 polypeptide, wherein that extracellular domain may comprise amino acids 1 to X of the sequence shown in Figure 24 (SEQ ID NO:59), where X is any amino acid from amino acid 216 to 225. Optionally, the PRO363 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA45419-1252 vector deposited on February 5, 1998 as ATCC 209616.

25 9. **PRO868**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to tumor necrosis factor receptor, wherein the polypeptide is designated in the present application as "PRO868".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO868 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO868 polypeptide having amino acid residues 1 to 655 of Figure 26 (SEQ ID NO:64), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO868 polypeptide having amino acid residues 1 to X of Figure 26 (SEQ ID NO:64), where X is any amino acid from amino acid 343 to 352 of the sequence shown in Figure 26 (SEQ ID NO:64), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In yet another aspect, the isolated nucleic acid comprises DNA encoding the PRO868 polypeptide having amino acid residues X to 655 of Figure 26 (SEQ ID NO:64), where X is any amino acid from amino acid 371 to 380 of the sequence shown in Figure 26 (SEQ ID NO:64), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated

nucleic acid sequence may comprise the cDNA insert of the DNA52594-1270 vector deposited on March 17, 1998 as ATCC 209679 which includes the nucleotide sequence encoding PRO868.

In another embodiment, the invention provides isolated PRO868 polypeptide. In particular, the invention provides isolated native sequence PRO868 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 655 of Figure 26 (SEQ ID NO:64). In another aspect, the isolated PRO868 polypeptide 5 comprises amino acid residues 1 to X of Figure 26 (SEQ ID NO:64), where X is any amino acid from amino acid 343 to 352 of the sequence shown in Figure 26 (SEQ ID NO:64). In yet another aspect, the PRO868 polypeptide comprises amino acid residues X to 655 of Figure 26 (SEQ ID NO:64), where X is any amino acid from amino acid 371 to 380 of the sequence shown in Figure 26 (SEQ ID NO:64). Optionally, the PRO868 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA52594-1270 vector deposited 10 on March 17, 1998 as ATCC 209679.

10. PRO382

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to serine proteases, wherein the polypeptide is designated in the present application as "PRO382".

15 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO382 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO382 polypeptide having amino acid residues 1 to 453 of Figure 28 (SEQ ID NO:69), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA45234-1277 vector 20 deposited on March 5, 1998 as ATCC 209654 which includes the nucleotide sequence encoding PRO382.

In another embodiment, the invention provides isolated PRO382 polypeptide. In particular, the invention provides isolated native sequence PRO382 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 453 of Figure 28 (SEQ ID NO:69). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO382 polypeptide, with or without the signal peptide. Optionally, 25 the PRO382 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA45234-1277 vector deposited on March 5, 1998 as ATCC 209654.

11. PRO545

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to meltrin, 30 wherein the polypeptide is designated in the present application as "PRO545".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO545 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO545 polypeptide having amino acid residues 1 to 735 of Figure 30 (SEQ ID NO:74), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency 35 conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 5, 1998 as ATCC 209655 which includes the nucleotide sequence encoding PRO545.

In another embodiment, the invention provides isolated PRO545 polypeptide. In particular, the invention provides isolated native sequence PRO545 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 735 of Figure 30 (SEQ ID NO:74). An additional embodiment of the present invention is

directed to an isolated extracellular domain of a PRO545 polypeptide. Optionally, the PRO545 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 5, 1998 as ATCC 209655.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13217 comprising the nucleotide sequence of SEQ ID NO:75 (Figure 31).

5

12. PRO617

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to CD24, wherein the polypeptide is designated in the present application as "PRO617".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a 10 PRO617 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO617 polypeptide having amino acid residues 1 to 67 of Figure 33 (SEQ ID NO:85), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA48309-1280 vector deposited on March 5, 1998 as ATCC 209656 which includes the nucleotide sequence encoding PRO617.

15 In another embodiment, the invention provides isolated PRO617 polypeptide. In particular, the invention provides isolated native sequence PRO617 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 67 of Figure 33 (SEQ ID NO:85). Optionally, the PRO617 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA48309-1280 vector deposited on March 5, 1998 as ATCC 209656.

20

13. PRO700

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to protein disulfide isomerase, wherein the polypeptide is designated in the present application as "PRO700".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a 25 PRO700 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO700 polypeptide having amino acid residues 1 to 432 of Figure 35 (SEQ ID NO:90), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO700 polypeptide having amino acid residues from about 34 to 432 of Figure 35 (SEQ ID NO:90), or is complementary to such encoding 30 nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 31, 1998 as ATCC 209721 which includes the nucleotide sequence encoding PRO700.

In another embodiment, the invention provides isolated PRO700 polypeptide. In particular, the invention provides isolated native sequence PRO700 polypeptide, which in one embodiment, includes an amino acid sequence 35 comprising residues 1 to 432 of Figure 35 (SEQ ID NO:90). In another embodiment, the invention provides an isolated PRO700 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues from about 34 to 432 of Figure 35 (SEQ ID NO:90). Optionally, the PRO700 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 31, 1998 as ATCC 209721.

14. PRO702

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to conglutinin, wherein the polypeptide is designated in the present application as "PRO702".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO702 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO702 polypeptide having amino acid residues 1 to 277 of Figure 37 (SEQ ID NO:97), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO702 polypeptide having amino acid residues 26 to 277 of Figure 37 (SEQ ID NO:97), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions.

10 The isolated nucleic acid sequence may comprise the cDNA insert of the DNA50980-1286 vector deposited on March 31, 1998 as ATCC 209717 which includes the nucleotide sequence encoding PRO702.

In another embodiment, the invention provides isolated PRO702 polypeptide. In particular, the invention provides isolated native sequence PRO702 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 277 of Figure 37 (SEQ ID NO:97). An additional embodiment of the present invention is directed to an isolated PRO702 polypeptide comprising amino acid residues 26 to 277 of Figure 37 (SEQ ID NO:97). Optionally, the PRO702 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA50980-1286 vector deposited on March 31, 1998 as ATCC 209717.

15. PRO703

20 Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to VLCAS, wherein the polypeptide is designated in the present application as "PRO703".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO703 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO703 polypeptide having amino acid residues 1 to 730 of Figure 39 (SEQ ID NO:102), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO703 polypeptide having amino acid residues from about 43 to 730 of Figure 39 (SEQ ID NO:102), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA50913-1287 vector deposited on March 31, 1998 as ATCC 209716 which includes the nucleotide sequence encoding PRO703.

In another embodiment, the invention provides isolated PRO703 polypeptide. In particular, the invention provides isolated native sequence PRO703 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 730 of Figure 39 (SEQ ID NO:102). In another embodiment, the invention provides an isolated PRO703 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues from about 43 to 730 of Figure 30 (SEQ ID NO:102). Optionally, the PRO703 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA50913-1287 vector deposited on March 31, 1998 as ATCC 209716.

16. PRO705

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to K-glycan, wherein the polypeptide is designated in the present application as "PRO705".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO705 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO705 polypeptide having amino acid residues 1 to 555 of Figure 41 (SEQ ID NO:109), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO705 polypeptide having amino acid residues about 24 to 555 of Figure 41 (SEQ ID NO:109), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA50914-1289 vector deposited on March 31, 1998 as ATCC 209722 which includes the nucleotide sequence encoding PRO705.

In another embodiment, the invention provides isolated PRO705 polypeptide. In particular, the invention provides isolated native sequence PRO705 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 555 of Figure 41 (SEQ ID NO:109). An additional embodiment of the present invention is directed to an isolated PRO705 polypeptide comprising amino acid residues about 24 to 555 of Figure 41 (SEQ ID NO:109). Optionally, the PRO705 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA50914-1289 vector deposited on March 31, 1998 as ATCC 209722.

17. PRO708

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the aryl sulfatases, wherein the polypeptide is designated in the present application as "PRO708".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO708 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO708 polypeptide having amino acid residues 1 to 515 of Figure 43 (SEQ ID NO:114), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA48296-1292 vector deposited on March 11, 1998 as ATCC 209668 which includes the nucleotide sequence encoding PRO708.

In another embodiment, the invention provides isolated PRO708 polypeptide. In particular, the invention provides isolated native sequence PRO708 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 515 of Figure 43 (SEQ ID NO:114). Another embodiment is directed to a PRO708 polypeptide comprising residues 38-515 of the amino acid sequence shown in Figure 43 (SEQ ID NO:114). Optionally, the PRO708 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA48296-1292 vector deposited on March 11, 1998 as ATCC 209668.

35 18. PRO320

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to fibulin, wherein the polypeptide is designated in the present application as "PRO320".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO320 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO320 polypeptide

having amino acid residues 1 to 338 of Figure 45 (SEQ ID NO:119), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 11, 1998 as ATCC 209670 which includes the nucleotide sequence encoding PRO320.

In another embodiment, the invention provides isolated PRO320 polypeptide. In particular, the invention 5 provides isolated native sequence PRO320 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 338 of Figure 45 (SEQ ID NO:119). Optionally, the PRO320 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 11, 1998 as ATCC 209670.

10 19. **PRO324**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to oxidoreductases, wherein the polypeptide is designated in the present application as "PRO324".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO324 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO324 polypeptide 15 having amino acid residues 1 to 289 of Figure 47 (SEQ ID NO:124), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO324 polypeptide having amino acid residues 1 or about 32 to X of Figure 47 (SEQ ID NO:124), where X is any amino acid from 131 to 140, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, 20 and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA36343-1310 vector deposited on March 30, 1998 as ATCC 209718 which includes the nucleotide sequence encoding PRO324.

In another embodiment, the invention provides isolated PRO324 polypeptide. In particular, the invention provides isolated native sequence PRO324 polypeptide, which in one embodiment, includes an amino acid sequence 25 comprising residues 1 to 289 of Figure 47 (SEQ ID NO:124). The invention also provides isolated PRO324 polypeptide comprising residues 1 or about 32 to X of Figure 47 (SEQ ID NO:124), wherein X is any amino acid from about 131-140. Optionally, the PRO324 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA36343-1310 vector deposited on March 30, 1998 as ATCC 209718.

30 20. **PRO351**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to prostasin, wherein the polypeptide is designated in the present application as "PRO351".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO351 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO351 polypeptide 35 having amino acid residues 1 to 571 of Figure 49 (SEQ ID NO:132), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO351 polypeptide having amino acid residues about 16 to 571 of Figure 49 (SEQ ID NO:132), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency

conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA40571-1315 vector deposited on April 21, 1998 as ATCC 209784 which includes the nucleotide sequence encoding PRO351.

In another embodiment, the invention provides isolated PRO351 polypeptide. In particular, the invention provides isolated native sequence PRO351 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 571 of Figure 49 (SEQ ID NO:132). In another embodiment, the invention provides an isolated PRO351 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues from about 16 to 571 of Figure 49 (SEQ ID NO:132). Optionally, the PRO351 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA40571-1315 vector deposited on April 21, 1998 as ATCC 209784.

10 21. **PRO352**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to butyrophilin, wherein the polypeptide is designated in the present application as "PRO352".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO352 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO352 polypeptide having amino acid residues 1 to 316 of Figure 51 (SEQ ID NO:137), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO352 polypeptide having amino acid residues of about 29 to 316 of Figure 51 (SEQ ID NO:137), or 1 or about 29 to X of Figure 51, where X is any amino acid from 246 to 255, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA41386-1316 vector deposited on March 26, 1998 as ATCC 209703 which includes the nucleotide sequence encoding PRO352.

In another embodiment, the invention provides isolated PRO352 polypeptide. In particular, the invention provides isolated native sequence PRO352 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 316 of Figure 51 (SEQ ID NO:137). In other embodiments, the invention provides isolated PRO352 polypeptide comprising residues about 29 to 316 of Figure 51 (SEQ ID NO:137) and 1 or about 29 to X of Figure 51 (SEQ ID NO:137), whercin X is any amino acid from 246 to 255. Optionally, the PRO352 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA41386-1316 vector deposited on March 26, 1998 as ATCC 209703.

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22. **PRO381**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to immunophilin proteins, wherein the polypeptide is designated in the present application as "PRO381".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO381 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO381 polypeptide having amino acid residues 1 to 211 of Figure 53 (SEQ ID NO:145), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO381 polypeptide having amino acid residues about 21 to 211 of Figure 53 (SEQ ID NO:145), or is complementary to such encoding nucleic

acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA44194-1317 vector deposited on April 28, 1998 as ATCC 209808 which includes the nucleotide sequence encoding PRO381.

In another embodiment, the invention provides isolated PRO381 polypeptide. In particular, the invention provides isolated native sequence PRO381 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 211 of Figure 53 (SEQ ID NO:145). Another embodiment is directed to a PRO381 polypeptide comprising amino acids about 21 to 211 of Figure 53 (SEQ ID NO:145). Optionally, the PRO381 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA44194-1317 vector deposited on April 28, 1998 as ATCC 209808.

10 23. **PRO386**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the beta-2 subunit of a sodium channel, wherein the polypeptide is designated in the present application as "PRO386".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO386 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO386 polypeptide having amino acid residues 1 to 215 of Figure 55 (SEQ ID NO:150), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO386 polypeptide having amino acid residues about 21 to 215 of Figure 55 (SEQ ID NO:150) or 1 or about 21 to X, where X is any amino acid from 156 to 165 of Figure 55 (SEQ ID NO:150), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA45415-1318 vector deposited on April 28, 1998 as ATCC 209810 which includes the nucleotide sequence encoding PRO386.

In another embodiment, the invention provides isolated PRO386 polypeptide. In particular, the invention provides isolated native sequence PRO386 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 215 of Figure 55 (SEQ ID NO:150). Other embodiments of the present invention are directed to PRO386 polypeptides comprising amino acids about 21 to 215 of Figure 55 (SEQ ID NO:150) and 1 or about 21 to X of Figure 55 (SEQ ID NO:150), wherein X is any amino acid from 156 to 165 of Figure 55 (SEQ ID NO:150). Optionally, the PRO386 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA45415-1318 vector deposited on April 28, 1998 as ATCC 209810.

30 In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of SEQ ID NO:151 which corresponds to an EST designated herein as DNA23350.

In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of SEQ ID NO:152 which corresponds to an EST designated herein as DNA23536.

35 24. **PRO540**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to LCAT, wherein the polypeptide is designated in the present application as "PRO540".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO540 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO540 polypeptide

having amino acid residues 1 to 412 of Figure 59 (SEQ ID NO:157), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO540 polypeptide having amino acid residues about 29 to 412 of Figure 59 (SEQ ID NO:157), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency 5 conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA44189-1322 vector deposited on March 26, 1998 as ATCC 209699 which includes the nucleotide sequence encoding PRO540.

In another embodiment, the invention provides isolated PRO540 polypeptide. In particular, the invention provides isolated native sequence PRO540 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 412 of Figure 59 (SEQ ID NO:157). The invention also provides isolated PRO540 10 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues about 29 to 412 of Figure 59 (SEQ ID NO:157). Optionally, the PRO540 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA44189-1322 vector deposited on March 26, 1998 as ATCC 209699.

15 25. **PRO615**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to synaptotyrin, wherein the polypeptide is designated in the present application as "PRO615".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO615 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO615 polypeptide 20 having amino acid residues 1 to 224 of Figure 61 (SEQ ID NO:162), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO615 polypeptide having amino acid residues X to 224 of Figure 61 (SEQ ID NO:162), where X is any amino acid from 157 to 166, or is 25 complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA48304-1323 vector deposited on April 28, 1998 as ATCC 209811 which includes the nucleotide sequence encoding PRO615.

In another embodiment, the invention provides isolated PRO615 polypeptide. In particular, the invention provides isolated native sequence PRO615 polypeptide, which in one embodiment, includes an amino acid sequence 30 comprising residues 1 to 224 of Figure 61 (SEQ ID NO:162). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO615 polypeptide which comprises amino acid residues X to 224 of Figure 61 (SEQ ID NO:162), where X is any amino acid from 157 to 166 of Figure 61 (SEQ ID NO:162). Optionally, the PRO615 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA 35 insert of the DNA48304-1323 vector deposited on April 28, 1998 as ATCC 209811.

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26. **PRO618**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to enteropeptidase, wherein the polypeptide is designated in the present application as "PRO618".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a

PRO618 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO618 polypeptide having amino acid residues 1 to 802 of Figure 63 (SEQ ID NO:169), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding an isolated extracellular domain of a PRO618 polypeptide having amino acid residues X to 802 of Figure 63 (SEQ ID NO:169), where X is any amino acid from 63 to 72 of Figure 63 (SEQ ID NO:169), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA49152-1324 vector deposited on April 28, 1998 as ATCC 209813 which includes the nucleotide sequence encoding PRO618.

In another embodiment, the invention provides isolated PRO618 polypeptide. In particular, the invention provides isolated native sequence PRO618 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 802 of Figure 63 (SEQ ID NO:169). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO618 polypeptide comprising amino acid X to 802 where X is any amino acid from 63 to 72 of Figure 63 (SEQ ID NO:169). Optionally, the PRO618 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA49152-1324 vector deposited on April 28, 1998 as ATCC 209813.

In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of SEQ ID NO:170, designated herein as DNA35597 (see Figure 64).

27. PRO719

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to lipoprotein lipase H, wherein the polypeptide is designated in the present application as "PRO719".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO719 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO719 polypeptide having amino acid residues 1 to 354 of Figure 66 (SEQ ID NO:178), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO719 polypeptide having amino acid residues about 17 to 354 of Figure 66 (SEQ ID NO:178), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA49646-1327 vector deposited on March 26, 1998 as ATCC 209705 which includes the nucleotide sequence encoding PRO719.

In another embodiment, the invention provides isolated PRO719 polypeptide. In particular, the invention provides isolated native sequence PRO719 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 354 of Figure 66 (SEQ ID NO:178). In another embodiment, the invention provides isolated PRO719 polypeptide which comprises residues about 17 to 354 of Figure 66 (SEQ ID NO:178). Optionally, the PRO719 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA49646-1327 vector deposited on March 26, 1998 as ATCC 209705.

28. PRO724

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the LDL receptor, wherein the polypeptide is designated in the present application as "PRO724".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO724 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO724 polypeptide having amino acid residues 1 to 713 of Figure 68 (SEQ ID NO:183), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding a soluble PRO724 polypeptide having amino acid residues 1 to X of Figure 68 (SEQ ID NO:183) where X is any amino acid from amino acid 437 to 446, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least 10 moderate, and optionally, under high stringency conditions. The above two polypeptides may either possess or not possess the signal peptide. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA49631-1328 vector deposited on April 28, 1998 as ATCC 209806 which includes the nucleotide sequence encoding PRO724.

In another embodiment, the invention provides isolated PRO724 polypeptide. In particular, the invention provides isolated native sequence PRO724 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 713 of Figure 68 (SEQ ID NO:183). In another embodiment, the invention provides isolated soluble PRO724 polypeptide. In particular, the invention provides isolated soluble PRO724 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to X of Figure 68 (SEQ ID NO:183), where X is any amino acid from 437 to 446 of the sequence shown in Figure 68 (SEQ ID NO:183). Optionally, the PRO724 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA49631-1328 vector deposited on April 28, 1998 as ATCC 209806.

29. PRO772

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to A4 protein, wherein the polypeptide is designated in the present application as "PRO772".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO772 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO772 polypeptide having amino acid residues 1 to 152 of Figure 70 (SEQ ID NO:190), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO772 polypeptide having amino acid residues 1 to X of Figure 70 (SEQ ID NO:190), where X is any amino acid from 21 to 30 of Figure 70 (SEQ ID NO:190), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA49645-1347 vector deposited on April 28, 1998 as ATCC 209809 which includes the nucleotide sequence encoding PRO772.

In another embodiment, the invention provides isolated PRO772 polypeptide. In particular, the invention provides isolated native sequence PRO772 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 152 of Figure 70 (SEQ ID NO:190). Additional embodiments of the present invention are directed to PRO772 polypeptides comprising amino acids 1 to X of Figure 70 (SEQ ID NO:190), where X is any amino acid from 21 to 30 of Figure 70 (SEQ ID NO:190). Optionally, the PRO772 polypeptide is obtained or is

obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA49645-1347 vector deposited on April 28, 1998 as ATCC 209809.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA43509 comprising the nucleotide sequence of SEQ ID NO:191 (Figure 71).

5 30. **PRO852**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to various protease enzymes, wherein the polypeptide is designated in the present application as "PRO852".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO852 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO852 polypeptide having amino acid residues 1 to 518 of Figure 73 (SEQ ID NO:196), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO852 polypeptide having amino acid residues about 21 to 518 of Figure 73 (SEQ ID NO:196) or 1 or about 21 to X of Figure 73 (SEQ ID NO:196) where X is any amino acid from amino acid 461 to amino acid 470 of Figure 73 (SEQ ID NO:196), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA45493-1349 vector deposited on April 28, 1998 as ATCC 209805 which includes the nucleotide sequence encoding PRO852.

In another embodiment, the invention provides isolated PRO852 polypeptide. In particular, the invention provides isolated native sequence PRO852 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 518 of Figure 73 (SEQ ID NO:196). In other embodiments, the PRO852 comprises amino acids about 21 to amino acid 518 of Figure 73 (SEQ ID NO:196) or amino acids 1 or about 21 to X of Figure 73 (SEQ ID NO:196), where X is any amino acid from amino acid 461 to amino acid 470 of Figure 73 (SEQ ID NO:196). Optionally, the PRO852 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA45493-1349 vector deposited on April 28, 1998 as ATCC 209805.

31. **PRO853**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to reductase, wherein the polypeptide is designated in the present application as "PRO853".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO853 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO853 polypeptide having amino acid residues 1 to 377 of Figure 75 (SEQ ID NO:206), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO853 polypeptide having amino acid residues about 17 to 377 of Figure 75 (SEQ ID NO:206), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA48227-1350 vector deposited on April 28, 1998 as ATCC 209812 which includes the nucleotide sequence encoding PRO853.

In another embodiment, the invention provides isolated PRO853 polypeptide. In particular, the invention

provides isolated native sequence PRO853 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 377 of Figure 75 (SEQ ID NO:206). In another embodiment, the invention provides an isolated PRO853 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues from about 17 to 377 of Figure 75 (SEQ ID NO:206). Optionally, the PRO853 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA48227-1350 vector deposited on
5 April 28, 1998 as ATCC 209812.

32. PRO860

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to neurofascin, wherein the polypeptide is designated in the present application as "PRO860".

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO860 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO860 polypeptide having amino acid residues 1 to 985 of Figure 77 (SEQ ID NO:211), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO860 polypeptide having
15 amino acid residues 1 to X of Figure 77 (SEQ ID NO:211), where X is any amino acid from 443-452 of Figure 77 (SEQ ID NO:211), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA41404-1352 vector deposited on May 6, 1998 as ATCC 209844 which includes the nucleotide sequence encoding PRO860.

20 In another embodiment, the invention provides isolated PRO860 polypeptide. In particular, the invention provides isolated native sequence PRO860 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 985 of Figure 77 (SEQ ID NO:211). In another embodiment, the invention provides an isolated PRO860 polypeptide which includes an amino acid sequence comprising residues 1 to X of Figure 77 (SEQ ID NO:211), where X is any amino acid residue from 443 to 452 of Figure 77 (SEQ ID NO:211). Optionally, the
25 PRO860 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA41404-1352 vector deposited on May 6, 1998 as ATCC 209844.

33. PRO846

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to
30 CMRF35, wherein the polypeptide is designated in the present application as "PRO846".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO846 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO846 polypeptide having amino acid residues 1 to 332 of Figure 79 (SEQ ID NO:216), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency
35 conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO846 polypeptide having amino acid residues about 18 to 332 of Figure 79 (SEQ ID NO:216) or 1 or about 18 to X of SEQ ID NO:216, where X is any amino acid from 243 to 252 of Figure 79 (SEQ ID NO:216), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA44196-1353 vector

deposited on May 6, 1998 as ATCC 209847 which includes the nucleotide sequence encoding PRO846.

In another embodiment, the invention provides isolated PRO846 polypeptide. In particular, the invention provides isolated native sequence PRO846 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 332 of Figure 79 (SEQ ID NO:216). In other embodiments, the invention provides an isolated PRO846 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues 5 from about 18 to 332 of Figure 79 (SEQ ID NO:216). Additional embodiments of the present invention are directed to an isolated PRO846 polypeptide comprising amino acid 1 or about 18 to X of Figure 79 (SEQ ID NO:216), where X is any amino acid from 243 to 252 of Figure 79 (SEQ ID NO:216). Optionally, the PRO846 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA44196-1353 vector deposited on May 6, 1998 as ATCC 209847.

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34. **PRO862**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to lysozyme, wherein the polypeptide is designated in the present application as "PRO862".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a 15 PRO862 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO862 polypeptide having amino acid residues 1 to 146 of Figure 81 (SEQ ID NO:221), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO862 polypeptide having 20 amino acid residues about 19 to 146 of Figure 81 (SEQ ID NO:221), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA52187-1354 vector deposited on May 6, 1998 as ATCC 209845 which includes the nucleotide sequence encoding PRO862.

In another embodiment, the invention provides isolated PRO862 polypeptide. In particular, the invention provides isolated native sequence PRO862 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 146 of Figure 81 (SEQ ID NO:221). In another embodiment, the invention provides an isolated PRO862 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues 25 from about 19 to 146 of Figure 81 (SEQ ID NO:221). Optionally, the PRO862 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA52187-1354 vector deposited on May 6, 1998 as ATCC 209845.

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35. **PRO864**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to Wnt-4, wherein the polypeptide is designated in the present application as "PRO864".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a 35 PRO864 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO864 polypeptide having amino acid residues 1 to 351 of Figure 83 (SEQ ID NO:226), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO864 polypeptide having amino acid residues about 23 to 351 of Figure 83 (SEQ ID NO:226), or is complementary to such encoding nucleic

acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA48328-1355 vector deposited on May 6, 1998 as ATCC 209843 which includes the nucleotide sequence encoding PRO864.

In another embodiment, the invention provides isolated PRO864 polypeptide. In particular, the invention provides isolated native sequence PRO864 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 351 of Figure 83 (SEQ ID NO:226). In another embodiment, the invention provides an isolated PRO864 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues from about 23 to 351 of Figure 83 (SEQ ID NO:226). Optionally, the PRO864 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA48328-1355 vector deposited on May 6, 1998 as ATCC 209843

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36. PRO792

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to CD23, wherein the polypeptide is designated in the present application as "PRO792".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO792 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO792 polypeptide having amino acid residues 1 to 293 of Figure 85 (SEQ ID NO:231), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO792 polypeptide having amino acid residues X to 293 of Figure 85 (SEQ ID NO:231) where X is any amino acid from 50 to 59 of Figure 85 (SEQ ID NO:231), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA56352-1358 vector deposited on May 6, 1998 as ATCC 209846 which includes the nucleotide sequence encoding PRO792.

In another embodiment, the invention provides isolated PRO792 polypeptide. In particular, the invention provides isolated native sequence PRO792 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 293 of Figure 85 (SEQ ID NO:231). An additional embodiment of the present invention is directed to PRO792 polypeptide comprising amino acids X to 293 of Figure 85 (SEQ ID NO:231), where X is any amino acid from 50 to 59 of Figure 85 (SEQ ID NO:231). Optionally, the PRO792 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA56352-1358 vector deposited on May 6, 1998 as ATCC 209846.

37. PRO866

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to mindin and spondin proteins, wherein the polypeptide is designated in the present application as "PRO866".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO866 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO866 polypeptide having amino acid residues 1 to 331 of Figure 87 (SEQ ID NO:236), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO866 polypeptide having

amino acid residues about 27 to 229 of Figure 87 (SEQ ID NO:236), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA53971-1359 vector deposited on April 7, 1998 as ATCC 209750 which includes the nucleotide sequence encoding PRO866.

In another embodiment, the invention provides isolated PRO866 polypeptide. In particular, the invention 5 provides isolated native sequence PRO866 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 331 of Figure 87 (SEQ ID NO:236). Another embodiment of the present invention is directed to PRO866 polypeptides comprising amino acids about 27 to 331 of Figure 87 (SEQ ID NO:236). Optionally, the PRO866 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA53971-1359 vector deposited on April 7, 1998 as ATCC 209750.

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38. PRO871

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to CyP-60, wherein the polypeptide is designated in the present application as "PRO871".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a 15 PRO871 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO871 polypeptide having amino acid residues 1 to 472 of Figure 89 (SEQ ID NO:245), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO871 polypeptide having amino acid residues about 22 to 472 of Figure 89 (SEQ ID NO:245), or is complementary to such encoding nucleic 20 acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA50919-1361 vector deposited on May 6, 1998 as ATCC 209848 which includes the nucleotide sequence encoding PRO871.

In another embodiment, the invention provides isolated PRO871 polypeptide. In particular, the invention provides isolated native sequence PRO871 polypeptide, which in one embodiment, includes an amino acid sequence 25 comprising residues 1 to 472 of Figure 89 (SEQ ID NO:245). An additional embodiment of the present invention is directed to PRO871 polypeptides comprising amino acids about 22 to 472 of Figure 89 (SEQ ID NO:245). Optionally, the PRO871 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA50919-1361 vector deposited on May 6, 1998 as ATCC 209848.

30 39. PRO873

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to carboxylesterase, wherein the polypeptide is designated in the present application as "PRO873".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a 35 PRO873 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO873 polypeptide having amino acid residues 1 to 545 of Figure 91 (SEQ ID NO:254), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO873 polypeptide having amino acid residues about 30 to about 545 of Figure 91 (SEQ ID NO:254), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency

conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA44179-1362 vector deposited on May 6, 1998 as ATCC 209851 which includes the nucleotide sequence encoding PRO873.

In another embodiment, the invention provides isolated PRO873 polypeptide. In particular, the invention provides isolated native sequence PRO873 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 545 of Figure 91 (SEQ ID NO:254). Additional embodiments of the present invention are 5 directed to PRO873 polypeptides comprising amino acids about 30 to about 545 of Figure 91 (SEQ ID NO:254). Optionally, the PRO873 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA44179-1362 vector deposited on May 6, 1998 as ATCC 209851.

40. **PRO940**

10 Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to CD33 and OB binding protein-2, wherein the polypeptide is designated in the present application as "PRO940".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO940 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO940 polypeptide having amino acid residues 1 to 544 of Figure 93 (SEQ ID NO:259), or is complementary to such encoding nucleic 15 acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO940 polypeptide having amino acid residues about 16 to 544 of Figure 93 (SEQ ID NO:259) or 1 or about 16 to X of Figure 93 (SEQ ID NO:259), where X is any amino acid from 394 to 403 of Figure 93 (SEQ ID NO:259), or is complementary to such 20 encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA54002-1367 vector deposited on April 7, 1998 as ATCC 209754 which includes the nucleotide sequence encoding PRO940.

In another embodiment, the invention provides isolated PRO940 polypeptide. In particular, the invention provides isolated native sequence PRO940 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 544 of Figure 93 (SEQ ID NO:259). Other embodiments of the present invention are 25 directed to PRO940 polypeptides comprising amino acids about 16 to 544 of Figure 93 (SEQ ID NO:259) or 1 or about 16 to X of Figure 93 (SEQ ID NO:259), where X is any amino acid from 394 to 403 of Figure 93 (SEQ ID NO:259). Optionally, the PRO940 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA54002-1367 vector deposited on April 7, 1998 as ATCC 209754.

30 41. **PRO941**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to a cadherin protein, wherein the polypeptide is designated in the present application as "PRO941".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO941 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO941 polypeptide 35 having amino acid residues 1 to 772 of Figure 95 (SEQ ID NO:264), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO941 polypeptide having amino acid residues about 22 to 772 of Figure 95 (SEQ ID NO:264) or 1 or about 22 to X of Figure 95 (SEQ ID NO:264), where X is any amino acid from 592 to 601 of Figure 95 (SEQ ID NO:264), or is complementary to such

encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA53906-1368 vector deposited on April 7, 1998 as ATCC 209747 which includes the nucleotide sequence encoding PRO941.

In another embodiment, the invention provides isolated PRO941 polypeptide. In particular, the invention provides isolated native sequence PRO941 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 772 of Figure 95 (SEQ ID NO:264). Additional embodiments of the present invention are directed to PRO941 polypeptides which comprise amino acid about 21 to 772 of Figure 95 (SEQ ID NO:264) or 1 or about 22 to X of Figure 95 (SEQ ID NO:264), where X is any amino acid from 592 to 601 of Figure 95 (SEQ ID NO:264). Optionally, the PRO941 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNAS53906-1368 vector deposited on April 7, 1998 as ATCC 209747.

10 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA6415 comprising the nucleotide sequence of Figure 96 (SEQ ID NO:265).

42. PRO944

15 Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to Clostridium perfringens enterotoxin receptor (CPE-R), wherein the polypeptide is designated in the present application as "PRO944".

20 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO944 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO944 polypeptide having amino acid residues 1 to 211 of Figure 98 (SEQ ID NO:270), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO944 polypeptide having amino acid residues about 22 to 229 of Figure 98 (SEQ ID NO:270) or amino acid 1 or about 22 to X of Figure 98 (SEQ ID NO:270) where X is any amino acid from 77 to 80 of Figure 98 (SEQ ID NO:270), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under 25 high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA52185-1370 vector deposited on May 14, 1998 as ATCC 209861 which includes the nucleotide sequence encoding PRO944.

30 In another embodiment, the invention provides isolated PRO944 polypeptide. In particular, the invention provides isolated native sequence PRO944 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 211 of Figure 98 (SEQ ID NO:270). Additional embodiments of the present invention are directed to PRO944 polypeptides comprising amino acids about 22 to 211 of Figure 98 (SEQ ID NO:270) or amino acid 1 or about 22 to X of Figure 98 (SEQ ID NO:270), where X is any amino acid from 77 to 86 of Figure 98 (SEQ ID NO:270). Optionally, the PRO944 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNAS52185-1370 vector deposited on May 14, 1998 as ATCC 209861.

35 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA14007 comprising the nucleotide sequence of Figure 99 (SEQ ID NO:271).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA12733 comprising the nucleotide sequence of Figure 100 (SEQ ID NO:272).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA12746 comprising the nucleotide sequence of Figure 101 (SEQ ID NO:273).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA12834 comprising the nucleotide sequence of Figure 102 (SEQ ID NO:274).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA12846 comprising the nucleotide sequence of Figure 103 (SEQ ID NO:275).

5 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13104 comprising the nucleotide sequence of Figure 104 (SEQ ID NO:276).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13259 comprising the nucleotide sequence of Figure 105 (SEQ ID NO:277).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13959 comprising the nucleotide sequence of Figure 106 (SEQ ID NO:278).

10 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13961 comprising the nucleotide sequence of Figure 107 (SEQ ID NO:279).

43. PRO983

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to a vesicle 15 associated protein, VAP-33, wherein the polypeptide is designated in the present application as "PRO983".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO983 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO983 polypeptide having amino acid residues 1 to 243 of Figure 109 (SEQ ID NO:284), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency 20 conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO983 polypeptide having amino acid residue 1 to X of Figure 109 (SEQ ID NO:284) where X is any amino acid from 219 to 228 of Figure 109 (SEQ ID NO:284), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA53977-1371 vector deposited on May 14, 1998 as ATCC 209862 which 25 includes the nucleotide sequence encoding PRO983.

In another embodiment, the invention provides isolated PRO983 polypeptide. In particular, the invention provides isolated native sequence PRO983 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 243 of Figure 109 (SEQ ID NO:284). Additional embodiments of the present invention are directed to PRO983 polypeptides comprising amino acid 1 to X of Figure 109 (SEQ ID NO:284), where X is any 30 amino acid from 219 to 228 of Figure 109 (SEQ ID NO:284). Optionally, the PRO983 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA53977-1371 vector deposited on May 14, 1998 as ATCC 209862.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA17130 comprising the nucleotide sequence of Figure 110 (SEQ ID NO:285).

35 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA23466 comprising the nucleotide sequence of Figure 111 (SEQ ID NO:286).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA26818 comprising the nucleotide sequence of Figure 112 (SEQ ID NO:287).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as

DNA37618 comprising the nucleotide sequence of Figure 113 (SEQ ID NO:288).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA41732 comprising the nucleotide sequence of Figure 114 (SEQ ID NO:289).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA45980 comprising the nucleotide sequence of Figure 115 (SEQ ID NO:290).

5 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA46372 comprising the nucleotide sequence of Figure 116 (SEQ ID NO:291).

44. PRO1057

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to proteases, 10 wherein the polypeptide is designated in the present application as "PRO1057".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1057 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1057 polypeptide having amino acid residues 1 to 413 of Figure 118 (SEQ ID NO:296), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency 15 conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1057 polypeptide having amino acid residues about 17 to 413 of Figure 118 (SEQ ID NO:296), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA57253-1382 vector deposited on May 14, 1998 as ATCC 209867 which includes the nucleotide sequence encoding PRO1057.

20 In another embodiment, the invention provides isolated PRO1057 polypeptide. In particular, the invention provides isolated native sequence PRO1057 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 413 of Figure 118 (SEQ ID NO:296). Additional embodiments of the present invention are directed to PRO1057 polypeptides comprising amino acids about 17 to 413 of Figure 118 (SEQ ID NO:296). Optionally, the PRO1057 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA 25 insert of the DNA57253-1382 vector deposited on May 14, 1998 as ATCC 209867.

45. PRO1071

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to thrombospondin, wherein the polypeptide is designated in the present application as "PRO1071".

30 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1071 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1071 polypeptide having amino acid residues 1 to 525 of Figure 120 (SEQ ID NO:301), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1071 polypeptide having 35 amino acid residues about 26 to 525 of Figure 120 (SEQ ID NO:301), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA58847-1383 vector deposited on May 20, 1998 as ATCC 209879 which includes the nucleotide sequence encoding PRO1071.

In another embodiment, the invention provides isolated PRO1071 polypeptide. In particular, the invention

provides isolated native sequence PRO1071 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 525 of Figure 120 (SEQ ID NO:301). Additional embodiments of the present invention are directed to PRO1071 polypeptides comprising amino acids about 26 to 525 of Figure 120 (SEQ ID NO:301). Optionally, the PRO1071 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA58847-1383 vector deposited on May 20, 1998 as ATCC 209879.

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46. PRO1072

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to reductase proteins, wherein the polypeptide is designated in the present application as "PRO1072".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a 10 PRO1072 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1072 polypeptide having amino acid residues 1 to 336 of Figure 122 (SEQ ID NO:303), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1072 polypeptide having amino acid residues about 22 to 336 of Figure 122 (SEQ ID NO:303), or is complementary to such encoding nucleic 15 acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA58747-1384 vector deposited on May 14, 1998 as ATCC 209868 which includes the nucleotide sequence encoding PRO1072.

In another embodiment, the invention provides isolated PRO1072 polypeptide. In particular, the invention provides isolated native sequence PRO1072 polypeptide, which in one embodiment, includes an amino acid sequence 20 comprising residues 1 to 336 of Figure 122 (SEQ ID NO:303). Additional embodiments of the present invention are directed to PRO1072 polypeptides comprising amino acids about 22 to 336 of Figure 122 (SEQ ID NO:303). Optionally, the PRO1072 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA58747-1384 vector deposited on May 14, 1998 as ATCC 209868.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as 25 DNA40210 comprising the nucleotide sequence of Figure 123 (SEQ ID NO:304).

47. PRO1075

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to protein disulfide isomerase, wherein the polypeptide is designated in the present application as "PRO1075".

30 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1075 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1075 polypeptide having amino acid residues 1 to 406 of Figure 125 (SEQ ID NO:309), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1075 polypeptide having 35 amino acid residues about 30 to 406 of Figure 125 (SEQ ID NO:309), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA57689-1385 vector deposited on May 14, 1998 as ATCC 209869 which includes the nucleotide sequence encoding PRO1075.

In another embodiment, the invention provides isolated PRO1075 polypeptide. In particular, the invention

provides isolated native sequence PRO1075 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 406 of Figure 125 (SEQ ID NO:309). Additional embodiments of the present invention are directed to PRO1075 polypeptides comprising amino acids about 30 to 406 of Figure 125 (SEQ ID NO:309). Optionally, the PRO1075 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNAS7689-1385 vector deposited on May 14, 1998 as ATCC 209869.

5 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13059 comprising the nucleotide sequence of Figure 126 (SEQ ID NO:310).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA19463 comprising the nucleotide sequence of Figure 127 (SEQ ID NO:311).

10 48. **PRO181**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the cornichon protein, wherein the polypeptide is designated in the present application as "PRO181".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO181 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO181 polypeptide having amino acid residues 1 to 144 of Figure 129 (SEQ ID NO:322), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO181 polypeptide having amino acid residues about 21 to 144 of Figure 129 (SEQ ID NO:322) or amino acid 1 or about 21 to X of Figure 129 (SEQ ID NO:322) where X is any amino acid from 52 to 61 of Figure 129 (SEQ ID NO:322), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA23330-1390 vector deposited on April 14, 1998 as ATCC 209775 which includes the nucleotide sequence encoding PRO181.

In another embodiment, the invention provides isolated PRO181 polypeptide. In particular, the invention provides isolated native sequence PRO181 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 144 of Figure 129 (SEQ ID NO:322). Additional embodiments of the present invention are directed to PRO181 polypeptides comprising amino acids about 21 to 144 of Figure 129 (SEQ ID NO:322) or amino acid 1 or about 21 to X of Figure 129 (SEQ ID NO:322), where X is any amino acid from 52 to 61 of Figure 129 (SEQ ID NO:322). Optionally, the PRO181 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA23330-1390 vector deposited on April 14, 1998 as ATCC 209775.

30 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13242 comprising the nucleotide sequence of Figure 130 (SEQ ID NO:323).

49. **PRO195**

Applicants have identified a cDNA clone that encodes a novel transmembrane polypeptide, wherein the 35 polypeptide is designated in the present application as "PRO195".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO195 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO195 polypeptide having amino acid residues 1 to 323 of Figure 132 (SEQ ID NO:330), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency

conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO195 polypeptide having amino acid residues about 32 to 323 of Figure 132 (SEQ ID NO:330) or amino acid 1 or about 32 to X of Figure 132 (SEQ ID NO:330) where X is any amino acid from 236 to 245 of Figure 132 (SEQ ID NO:330), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA26847-1395 vector deposited on April 14, 1998 as ATCC 209772 which includes the nucleotide sequence encoding PRO195.

5 In another embodiment, the invention provides isolated PRO195 polypeptide. In particular, the invention provides isolated native sequence PRO195 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 323 of Figure 132 (SEQ ID NO:330). Additional embodiments of the present invention are directed to PRO195 polypeptides comprising amino acids about 32 to 323 of Figure 132 (SEQ ID NO:330) or amino 10 acid 1 or about 32 to X of Figure 132 (SEQ ID NO:330), where X is any amino acid from 236 to 245 of Figure 132 (SEQ ID NO:330). Optionally, the PRO195 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA26847-1395 vector deposited on April 14, 1998 as ATCC 209772.

10 In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of Figure 133 (SEQ ID NO:331), herein designated DNA15062.

15 In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of Figure 134 (SEQ ID NO:332), herein designated DNA13199.

50. **PRO865**

Applicants have identified a cDNA clone that encodes a novel secreted polypeptide, wherein the polypeptide 20 is designated in the present application as "PRO865".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO865 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO865 polypeptide having amino acid residues 1 to 468 of Figure 136 (SEQ ID NO:337), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency 25 conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO865 polypeptide having amino acid residues about 24 to 229 of Figure 136 (SEQ ID NO:337), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNAS3974-1401 vector deposited on April 14, 1998 as ATCC 209774 which includes the nucleotide sequence encoding PRO865.

30 In another embodiment, the invention provides isolated PRO865 polypeptide. In particular, the invention provides isolated native sequence PRO865 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 468 of Figure 136 (SEQ ID NO:337). An additional embodiment of the present invention is directed to a PRO865 polypeptide comprising amino acids about 24 to 468 of Figure 136 (SEQ ID NO:337). Optionally, the PRO865 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA 35 insert of the DNAS3974-1401 vector deposited on April 14, 1998 as ATCC 209774.

In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of Figure 137 (SEQ ID NO:338), herein designated as DNA37642.

51. PRO827

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to integrin proteins, wherein the polypeptide is designated in the present application as "PRO827".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO827 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO827 polypeptide having amino acid residues 1 to 124 of Figure 139 (SEQ ID NO:346), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO827 polypeptide having amino acid residues about 23 to 124 of Figure 139 (SEQ ID NO:346), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA57039-1402 vector deposited on April 14, 1998 as ATCC 209777 which includes the nucleotide sequence encoding PRO827.

In another embodiment, the invention provides isolated PRO827 polypeptide. In particular, the invention provides isolated native sequence PRO827 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 124 of Figure 139 (SEQ ID NO:346). An additional embodiment of the present invention is directed to a PRO827 polypeptide comprising amino acids about 23 to 124 of Figure 139 (SEQ ID NO:346). Optionally, the PRO827 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA57039-1402 vector deposited on April 14, 1998 as ATCC 209777.

52. PRO1114

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to cytokine receptor family-4 proteins, wherein the polypeptide is designated in the present application as "PRO1114".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1114 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1114 polypeptide having amino acid residues 1 to 311 of Figure 142 (SEQ ID NO:352), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1114 polypeptide having amino acid residues about 30 to 311 of Figure 142 (SEQ ID NO:352) or amino acid 1 or about 30 to X of Figure 142 (SEQ ID NO:352), where X is any amino acid from 225 to 234 of Figure 142 (SEQ ID NO:352), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA57033-1403 vector deposited on May 27, 1998 as ATCC 209905 which includes the nucleotide sequence encoding PRO1114.

In another embodiment, the invention provides isolated PRO1114 polypeptide. In particular, the invention provides isolated native sequence PRO1114 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 311 of Figure 142 (SEQ ID NO:352). Additional embodiments of the present invention are directed to PRO1114 polypeptides comprising amino acids about 30 to 311 of Figure 142 (SEQ ID NO:352) or amino acid 1 or about 30 to X of Figure 142 (SEQ ID NO:352), where X is any amino acid from 225 to 234 of Figure 142 (SEQ ID NO:352). Optionally, the PRO1114 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA57033-1403 vector deposited on May 27, 1998 as ATCC 209905.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA48466 comprising the nucleotide sequence of Figure 143 (SEQ ID NO:353).

A cDNA clone (DNA57033-1403) has been identified that encodes a novel interferon receptor polypeptide, designated in the present application as "PRO1114 interferon receptor".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1114 interferon receptor polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1114 interferon receptor polypeptide having the sequence of amino acid residues from about 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1114 interferon receptor polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 250 or about 337 and about 1182, inclusive, of Figure 141 (SEQ ID NO:351). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209905 (DNA57033-1403) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209905 (DNA57033-1403).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1114 interferon receptor polypeptide having the sequence of amino acid residues from 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1114 interferon receptor polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 29 in the sequence of Figure 142 (SEQ ID NO:352). The transmembrane domain has been tentatively identified as extending from about amino acid position 230 to about amino acid position

255 in the PRO1114 interferon receptor amino acid sequence (Figure 142, SEQ ID NO:352).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1114 interferon receptor polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from 10 the nucleotide sequence shown in Figure 141 (SEQ ID NO:351).

In another embodiment, the invention provides a vector comprising DNA encoding PRO1114 interferon receptor or its variants. The vector may comprise any of the isolated nucleic acid molecules hereinabove identified.

A host cell comprising such a vector is also provided. By way of example, the host cells may be CHO cells, 15 E. coli, or yeast. A process for producing PRO1114 interferon receptor polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of PRO1114 interferon receptor and recovering PRO1114 interferon receptor from the cell culture.

In another embodiment, the invention provides isolated PRO1114 interferon receptor polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1114 interferon receptor 20 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 30 to about 311 of Figure 142 (SEQ ID NO:352).

In another aspect, the invention concerns an isolated PRO1114 interferon receptor polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the 25 sequence of amino acid residues 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352).

In a further aspect, the invention concerns an isolated PRO1114 interferon receptor polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352).

30 In yet another aspect, the invention concerns an isolated PRO1114 interferon receptor polypeptide, comprising the sequence of amino acid residues 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352), or a fragment thereof sufficient to provide a binding site for an anti-PRO1114 interferon receptor antibody. Preferably, the PRO1114 interferon receptor fragment retains a qualitative biological activity of a native PRO1114 interferon receptor polypeptide.

35 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1114 interferon receptor polypeptide having the sequence of amino acid residues from about 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence

identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In another embodiment, the invention provides chimeric molecules comprising a PRO1114 interferon receptor polypeptide fused to a heterologous polypeptide or amino acid sequence. An example of such a chimeric molecule comprises a PRO1114 interferon receptor polypeptide fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which specifically binds to a PRO1114 interferon receptor polypeptide. Optionally, the antibody is a monoclonal antibody.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1114 interferon receptor polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1114 interferon receptor antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1114 interferon receptor polypeptide by contacting the native PRO1114 interferon receptor polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1114 interferon receptor polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

53. **PRO237**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to carbonic anhydrase, wherein the polypeptide is designated in the present application as "PRO237".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO237 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO237 polypeptide having amino acid residues 1 to 328 of Figure 145 (SEQ ID NO:358), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO237 polypeptide having amino acid residues about 24 to 328 of Figure 145 (SEQ ID NO:358) or amino acid 1 or about 24 to X of Figure 145 (SEQ ID NO:358), where X is any amino acid from 172 to 181 of Figure 145 (SEQ ID NO:358), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA34353-1428 vector deposited on May 12, 1998 as ATCC 209855 which includes the nucleotide sequence encoding PRO237.

In another embodiment, the invention provides isolated PRO237 polypeptide. In particular, the invention provides isolated native sequence PRO237 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 328 of Figure 145 (SEQ ID NO:358). Additional embodiments of the present invention are directed to PRO237 polypeptides comprising amino acids about 24 to 328 of Figure 145 (SEQ ID NO:358) or amino acid 1 or about 24 to X of Figure 145 (SEQ ID NO:358), where X is any amino acid from 172 to 181 of Figure 145 (SEQ ID NO:358). Optionally, the PRO237 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA34353-1428 vector deposited on May 12, 1998 as ATCC 209855.

54. PRO541

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to a trypsin inhibitor protein, wherein the polypeptide is designated in the present application as "PRO541".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO541 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO541 polypeptide having amino acid residues 1 to 500 of Figure 147 (SEQ ID NO:363), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO541 polypeptide having amino acid residues about 21 to 500 of Figure 147 (SEQ ID NO:363), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA45417-1432 vector deposited on May 27, 1998 as ATCC 209910 which includes the nucleotide sequence encoding PRO541.

In another embodiment, the invention provides isolated PRO541 polypeptide. In particular, the invention provides isolated native sequence PRO541 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 500 of Figure 147 (SEQ ID NO:363). Additional embodiments of the present invention are directed to PRO541 polypeptides comprising amino acids about 21 to 500 of Figure 147 (SEQ ID NO:363). Optionally, the PRO541 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA45417-1432 vector deposited on May 27, 1998 as ATCC 209910.

55. PRO273

Applicants have identified a cDNA clone that encodes a novel polypeptide, wherein the polypeptide is designated in the present application as "PRO273".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO273 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO273 polypeptide having amino acid residues 1 through 111 of Figure 149 (SEQ ID NO:370), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions.

In another embodiment, the invention provides isolated PRO273 polypeptide. In particular, the invention provides isolated native sequence PRO273 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 111 of Figure 149 (SEQ ID NO:370).

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56. PRO701

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to neuroligins 1, 2, and 3, wherein the polypeptide is designated in the present application as "PRO701".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO701 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO701 polypeptide having amino acid residues 1 through 816 of Figure 151 (SEQ ID NO:375), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited with the ATCC on March 31, 1998 which includes the nucleotide sequence encoding PRO701.

In another embodiment, the invention provides isolated PRO701 polypeptide. In particular, the invention provides isolated native sequence PRO701 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 816 of Figure 151 (SEQ ID NO:375). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO701 polypeptide. Optionally, the PRO701 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector 5 deposited with the ATCC on March 31, 1998.

57. PRO704

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with VIP36, wherein the polypeptide is designated in the present application as "PRO704".

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO704 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO704 polypeptide having amino acid residues 1 through 348 of Figure 153 (SEQ ID NO:380), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 31, 15 1998 with the ATCC as DNA50911-1288, which includes the nucleotide sequence encoding PRO704.

In another embodiment, the invention provides isolated PRO704 polypeptide. In particular, the invention provides isolated native sequence PRO704 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 348 of Figure 153 (SEQ ID NO:380). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO704 polypeptide. Optionally, the PRO704 20 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 31, 1998 with the ATCC as DNA50911-1288.

58. PRO706

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to prostatic acid 25 phosphatase precursor and lysosomal acid phosphatase precursor, wherein the polypeptide is designated in the present application as "PRO706".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO706 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO706 polypeptide having amino acid residues 1 through 480 of Figure 155 (SEQ ID NO:385), or is complementary to such encoding 30 nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on April 21, 1998 with the ATCC as DNA48329-1290 which includes the nucleotide sequence encoding PRO706.

In another embodiment, the invention provides isolated PRO706 polypeptide. In particular, the invention provides isolated native sequence PRO706 polypeptide, which in one embodiment, includes an amino acid sequence 35 comprising residues 1 through 480 of Figure 155 (SEQ ID NO:385), or comprising residues 19 through 480 of Figure 155 (SEQ ID NO:385). Optionally, the PRO706 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on April 21, 1998 with the ATCC as DNA48329-1290.

59. PRO707

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to cadherins, particularly cadherin FIB3, wherein the polypeptide is designated in the present application as "PRO707".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO707 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO707 polypeptide having amino acid residues 1 to 916 of Figure 157 (SEQ ID NO:390), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on May 27, 1998 with the ATCC as DNA48306-1291 which includes the nucleotide sequence encoding PRO707.

In another embodiment, the invention provides isolated PRO707 polypeptide. In particular, the invention provides isolated native sequence PRO707 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 916 of Figure 157 (SEQ ID NO:390). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO707 polypeptide. Optionally, the PRO707 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on May 27, 1998 with the ATCC as DNA48306-1291.

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60. PRO322

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to neuropsin, wherein the polypeptide is designated in the present application as "PRO322".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO322 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO322 polypeptide having amino acid residues 1 or 24 through 260 of Figure 159 (SEQ ID NO:395), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 11, 1998 as ATCC no. 209669 which includes the nucleotide sequence encoding PRO322.

25 In another embodiment, the invention provides isolated PRO322 polypeptide. In particular, the invention provides isolated native sequence PRO322 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 24 through 260 of Figure 159 (SEQ ID NO:395). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO322 polypeptide. Optionally, the PRO322 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 11, 1998 as ATCC no. 209669.

61. PRO526

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with ALS, wherein the polypeptide is designated in the present application as "PRO526".

35 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO526 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO526 polypeptide having amino acid residues 1 to 473 of Figure 161 (SEQ ID NO:400), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 26,

1998 with the ATCC as DNA44184-1319 which includes the nucleotide sequence encoding PRO526.

In another embodiment, the invention provides isolated PRO526 polypeptide. In particular, the invention provides isolated native sequence PRO526 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 473 of Figure 161 (SEQ ID NO:400). Optionally, the PRO526 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 26, 1998
5 with the ATCC as DNA44184-1319 which includes the nucleotide sequence encoding PRO526.

62. **PRO531**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with protocadherins, wherein the polypeptide is designated in the present application as "PRO531".

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO531 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO531 polypeptide having amino acid residues 1 to 789 of Figure 163 (SEQ ID NO:405), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 26,
15 1998 as DNA48314-1320 which includes the nucleotide sequence encoding PRO531.

In another embodiment, the invention provides isolated PRO531 polypeptide. In particular, the invention provides isolated native sequence PRO531 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 789 of Figure 163 (SEQ ID NO:405). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO531 polypeptide. Optionally, the PRO531 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 26, 1998 as DNA48314-1320.

63. **PRO534**

25 Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with disulfide isomerase (sometimes referred to herein as protein disulfide isomerase), wherein the polypeptide is designated in the present application as "PRO534".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO534 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO534 polypeptide having amino acid residues 1 to 360 of Figure 165 (SEQ ID NO:410), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 26, 1998 as DNA48333-1321 which includes the nucleotide sequence encoding PRO534.

30 In another embodiment, the invention provides isolated PRO534 polypeptide. In particular, the invention provides isolated native sequence PRO534 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 360 of Figure 165 (SEQ ID NO:410). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO534 polypeptide. Optionally, the PRO534 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 26, 1998 as DNA48333-1321.

64. PRO697

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with sFRPs, wherein the polypeptide is designated in the present application as "PRO697".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO697 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO697 polypeptide having amino acid residues 1 through 295 of Figure 167 (SEQ ID NO:415), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited with the ATCC on March 26, 1998 as DNA50920-1325 which includes the nucleotide sequence encoding PRO697.

In another embodiment, the invention provides isolated PRO697 polypeptide. In particular, the invention provides isolated native sequence PRO697 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 295 of Figure 167 (SEQ ID NO:415). Optionally, the PRO697 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited with the ATCC on March 26, 1998 as DNA50920-1325.

15 65. PRO717

Applicants have identified a cDNA clone that encodes a novel 12 transmembrane polypeptide, wherein the polypeptide is designated in the present application as "PRO717".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO717 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO717 polypeptide having amino acid residues 1 through 560 of Figure 169 (SEQ ID NO:420), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on April 28, 1998 with the ATCC as DNA50988-1326 which includes the nucleotide sequence encoding PRO717.

In another embodiment, the invention provides isolated PRO717 polypeptide. In particular, the invention provides isolated native sequence PRO717 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 560 of Figure 169 (SEQ ID NO:420). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO717 polypeptide. Optionally, the PRO717 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on April 28, 1998 with the ATCC as DNA50988-1326.

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66. PRO731

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with protocadherin 4, wherein the polypeptide is designated in the present application as "PRO731".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO731 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO731 polypeptide having amino acid residues 1 through 1184 of Figure 171 (SEQ ID NO:425), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 31, 1998 with the ATCC as DNA48331-1329 which includes the nucleotide sequence encoding PRO731.

In another embodiment, the invention provides isolated PRO731 polypeptide. In particular, the invention provides isolated native sequence PRO731 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 1184 of Figure 171 (SEQ ID NO:425). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO731 polypeptide. Optionally, the PRO731 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 31, 1998 with the ATCC as DNA48331-1329.

67. PRO218

Applicants have identified a cDNA clone that encodes a novel multi-transmembrane protein having sequence identity with membrane regulator proteins, wherein the polypeptide is designated in the present application as "PRO218".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO218 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO218 polypeptide having amino acid residues 1 through 455 of Figure 173 (SEQ ID NO:430), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on April 28, 1998 with the ATCC as DNA30867-1335 which includes the nucleotide sequence encoding PRO218.

In another embodiment, the invention provides isolated PRO218 polypeptide. In particular, the invention provides isolated native sequence PRO218 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 455 of Figure 173 (SEQ ID NO:430). Optionally, the PRO218 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on April 28, 1998 with the ATCC as DNA30867-1335.

In another embodiment, the invention provides an expressed sequence tag (EST) sequence comprising the nucleotide sequence of Figure 174 (SEQ ID NO:431), designated herein as DNA14472.

In another embodiment, the invention provides an expressed sequence tag (EST) sequence comprising the nucleotide sequence of Figure 175 (SEQ ID NO:432), designated herein as DNA15846.

68. PRO768

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with integrins, wherein the polypeptide is designated in the present application as "PRO768".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO768 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO768 polypeptide having amino acid residues 1 through 1141 of Figure 177 (SEQ ID NO:437), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on April 6, 1998 as DNA55737-1345 which includes the nucleotide sequence encoding PRO768.

In another embodiment, the invention provides isolated PRO768 polypeptide. In particular, the invention provides isolated native sequence PRO768 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 1141 of Figure 177 (SEQ ID NO:437). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO768 polypeptide. Optionally, the PRO768

polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on April 6, 1998 as DNA55737-1345.

69. **PRO771**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with 5 testican, wherein the polypeptide is designated in the present application as "PRO771".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO771 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO771 polypeptide having amino acid residues 1 through 436 of Figure 179 (SEQ ID NO:442), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency 10 conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on April 7, 1998 with the ATCC as DNA49829-1346 which includes the nucleotide sequence encoding PRO771.

In another embodiment, the invention provides isolated PRO771 polypeptide. In particular, the invention provides isolated native sequence PRO771 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 436 of Figure 179 (SEQ ID NO:442). Optionally, the PRO771 polypeptide is obtained 15 or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on April 7, 1998 with the ATCC as DNA49829-1346.

70. **PRO733**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with 20 the T1/ST2 receptor binding protein, wherein the polypeptide is designated in the present application as "PRO733".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO733 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO733 polypeptide having amino acid residues 1 through 229 of Figure 181 (SEQ ID NO:447), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency 25 conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on April 7, 1998 with the ATCC as DNA52196-1348 which includes the nucleotide sequence encoding PRO733.

In another embodiment, the invention provides isolated PRO733 polypeptide. In particular, the invention provides isolated native sequence PRO733 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 229 of Figure 181 (SEQ ID NO:447). An additional embodiment of the present 30 invention is directed to an isolated extracellular domain of a PRO733 polypeptide. Optionally, the PRO733 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on April 7, 1998 as DNA52196-1348.

71. **PRO162**

35 Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with pancreatitis-associated protein, wherein the polypeptide is designated in the present application as "PRO162".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO162 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO162 polypeptide having amino acid residues 1 through 175 of Figure 183 (SEQ ID NO:452), or is complementary to such encoding

nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on May 6, 1998 with the ATCC as DNA56965-1356 which includes the nucleotide sequence encoding PRO162.

In another embodiment, the invention provides isolated PRO162 polypeptide. In particular, the invention provides isolated native sequence PRO162 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 175 of Figure 183 (SEQ ID NO:452). Optionally, the PRO162 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on May 6, 1998 with the ATCC as DNA56965-1356.

72. **PRO788**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with anti-neoplastic urinary protein, wherein the polypeptide is designated in the present application as "PRO788".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO788 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO788 polypeptide having amino acid residues 1 through 125 of Figure 185 (SEQ ID NO:454), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on May 6, 1998 with the ATCC as DNA56405-1357 which includes the nucleotide sequence encoding PRO788.

In another embodiment, the invention provides isolated PRO788 polypeptide. In particular, the invention provides isolated native sequence PRO788 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 125 of Figure 185 (SEQ ID NO:454). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO788 polypeptide. Optionally, the PRO788 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on May 6, 1998 with the ATCC as DNA56405-1357.

25 73. **PRO1008**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with dickkopf-1 (dkk-1), wherein the polypeptide is designated in the present application as "PRO1008".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1008 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1008 polypeptide having amino acid residues 1 through 266 of Figure 187 (SEQ ID NO:456), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on May 20, 1998 with the ATCC as DNA57530-1375 which includes the nucleotide sequence encoding PRO1008.

In another embodiment, the invention provides isolated PRO1008 polypeptide. In particular, the invention provides isolated native sequence PRO1008 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 266 of Figure 187 (SEQ ID NO:456). Optionally, the PRO1008 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on May 20, 1998 with the ATCC as DNA57530-1375.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA16508 comprising the nucleotide sequence of Figure 188 (SEQ ID NO:457).

74. **PRO1012**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with disulfide isomerase and phospholipase C, wherein the polypeptide is designated in the present application as "PRO1012".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1012 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1012 polypeptide having amino acid residues 1 through 747 of Figure 190 (SEQ ID NO:459), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on May 14, 1998 with the ATCC as DNA56439-1376, which includes the nucleotide sequence encoding PRO1012.

In another embodiment, the invention provides isolated PRO1012 polypeptide. In particular, the invention provides isolated native sequence PRO1012 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 747 of Figure 190 (SEQ ID NO:459). Optionally, the PRO1012 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on May 14, 1998 with the ATCC as DNA56439-1376.

75. **PRO1014**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with reductase, wherein the polypeptide is designated in the present application as "PRO1014".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1014 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1014 polypeptide having amino acid residues 1 through 300 of Figure 192 (SEQ ID NO:464), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on May 20, 1998 as DNA56409-1377 with the ATCC which includes the nucleotide sequence encoding PRO1014.

In another embodiment, the invention provides isolated PRO1014 polypeptide. In particular, the invention provides isolated native sequence PRO1014 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 300 of Figure 192 (SEQ ID NO:464). Optionally, the PRO1014 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on May 20, 1998 as DNA56409-1377 with the ATCC.

76. **PRO1017**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with HNK-1 sulfotransferase, wherein the polypeptide is designated in the present application as "PRO1017".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1017 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1017 polypeptide having amino acid residues 1 through 414 of Figure 194 (SEQ ID NO:466), or is complementary to such encoding

nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on May 20, 1998 with the ATCC as DNA56112-1379 which includes the nucleotide sequence encoding PRO1017.

In another embodiment, the invention provides isolated PRO1017 polypeptide. In particular, the invention provides isolated native sequence PRO1017 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 414 of Figure 194 (SEQ ID NO:466). Optionally, the PRO1017 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on May 20, 1998 with the ATCC as DNA56112-1379.

77. PRO474

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with dehydrogenase, wherein the polypeptide is designated in the present application as "PRO474".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO474 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO474 polypeptide having amino acid residues 1 through 270 of Figure 196 (SEQ ID NO:468), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on May 14, 1998 with the ATCC as DNA56045-1380 which includes the nucleotide sequence encoding PRO474.

In another embodiment, the invention provides isolated PRO474 polypeptide. In particular, the invention provides isolated native sequence PRO474 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 270 of Figure 196 (SEQ ID NO:468). Optionally, the PRO474 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on May 14, 1998 with the ATCC as DNA56045-1380.

78. PRO1031

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with IL-17, wherein the polypeptide is designated in the present application as "PRO1031".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1031 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1031 polypeptide having amino acid residues 1 through 180 of Figure 198 (SEQ ID NO:470), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on May 14, 1998 with the ATCC as DNA59294-1381 which includes the nucleotide sequence encoding PRO1031.

In another embodiment, the invention provides isolated PRO1031 polypeptide. In particular, the invention provides isolated native sequence PRO1031 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 180 of Figure 198 (SEQ ID NO:470). Optionally, the PRO1031 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on May 14, 1998 with the ATCC as DNA59294-1381.

79. PRO938

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity to protein disulfide isomerase, wherein the polypeptide is designated in the present application as "PRO938".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO938 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO938 polypeptide having amino acid residues 1 to 349 of Figure 200 (SEQ ID NO:472), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO938 polypeptide having amino acid residues about 23 to 349 of Figure 200 (SEQ ID NO:472) or amino acid 1 or about 23 to X of Figure 200 (SEQ ID NO:472), where X is any amino acid from 186 to 195 of Figure 200 (SEQ ID NO:472), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA56433-1406 vector deposited on May 12, 1998, as ATCC Accession No. 209857 which includes the nucleotide sequence encoding PRO938.

In another embodiment, the invention provides isolated PRO938 polypeptide. In particular, the invention provides isolated native sequence PRO938 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 349 of Figure 200 (SEQ ID NO:472). Additional embodiments of the present invention are directed to PRO938 polypeptides comprising amino acids about 23 to 349 of Figure 200 (SEQ ID NO:472) or amino acid 1 or about 23 to X of Figure 200 (SEQ ID NO:472), where X is any amino acid from 186 to 195 of Figure 200 (SEQ ID NO:472). Optionally, the PRO938 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA56433-1406 vector deposited on May 12, 1998, as ATCC Accession No. 209857.

80. PRO1082

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with a lectin-like oxidized LDL receptor, wherein the polypeptide is designated in the present application as "PRO1082".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1082 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1082 polypeptide having amino acid residues 1 through 201 of Figure 202 (SEQ ID NO:477), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on May 14, 1998 with the ATCC as DNA53912-1457 which includes the nucleotide sequence encoding PRO1082.

In another embodiment, the invention provides isolated PRO1082 polypeptide. In particular, the invention provides isolated native sequence PRO1082 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 201 of Figure 202 (SEQ ID NO:477). An additional embodiment of the present invention is directed to an isolated domain of a PRO1082 polypeptide, excluding the transmembrane domain. Optionally, the PRO1082 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on May 14, 1998 with the ATCC as DNA53912-1457.

81. PRO1083

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with a 7TM receptor, latrophilin-related protein 1, and a macrophage restricted cell surface glycoprotein, wherein the polypeptide is designated in the present application as "PRO1083".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1083 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1083 polypeptide having amino acid residues 1 through 693 of Figure 204 (SEQ ID NO:483), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on May 12, 1998 with the ATCC as DNA50921-1458 which includes the nucleotide sequence encoding PRO1083.

10 In another embodiment, the invention provides isolated PRO1083 polypeptide. In particular, the invention provides isolated native sequence PRO1083 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 693 of Figure 204 (SEQ ID NO:483). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO1083 polypeptide. Optionally, the PRO1083 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector 15 deposited on May 12, 1998 with the ATCC as DNA50921-1458.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA24256 which comprises the nucleotide sequence of Figure 205 (SEQ ID NO:484).

82. PRO200

20 The objects of this invention, as defined generally supra, are achieved at least in part by the provision of a novel polypeptide, VEGF-E also herein designated PRO200, (SEQ ID NO:488) and the nucleic acid encoding therefor, SEQ ID NO:487, residues 259 through 1293.

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a VEGF-E polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the VEGF-E polypeptide 25 having amino acid residues 1 through 345 of Figure 207 (SEQ ID NO:488), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under low stringency conditions. In another embodiment, variants are provided wherein the VEGF-E nucleic acid has single or multiple deletions, substitutions, insertions, truncations or combinations thereof.

30 In another embodiment, the invention provides isolated VEGF-E polypeptide. In particular, the invention provides an isolated native sequence VEGF-E polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 345 of Figure 207 (SEQ ID NO:488). In another embodiment, variants are provided wherein the VEGF-E polypeptide has single or multiple deletions, substitutions, insertions, truncations or combinations thereof.

35 In yet further embodiments, the present invention is directed to compositions useful for treating indications where proliferation, survival and/or differentiation of cells is desired, comprising a therapeutically effective amount of a VEGF-E polypeptide hereof in admixture with a pharmaceutically acceptable carrier.

The invention further includes associated embodiments of VEGF-E such as modified VEGF-E polypeptides and modified variants which have the same biological applications as VEGF-E, and pharmaceutical compositions incorporating same. Inhibitors of VEGF-E are also provided.

83. **PRO285 and PRO286**

Applicants have identified two novel cDNA clones that encode novel human Toll polypeptides, designated in the present application as PRO285 (encoded by DNA40021-1154) and PRO286 (encoded by DNA42663-1154).

In one embodiment, the invention provides an isolated nucleic acid molecule comprising a DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO285 polypeptide having amino acid residues 27 to 839 of Figure 209 (SEQ ID NO:496); or (b) to a DNA molecule encoding a PRO286 polypeptide having amino acid residues 27 to 825 of Figure 211 (SEQ ID NO:498) or (c) the complement of the DNA molecule of (a) or (b). The complementary DNA molecule preferably remains stably bound to such encoding nucleic acid sequence under at least moderate, and optionally, under high stringency conditions.

In a further embodiment, the isolated nucleic acid molecule comprises a polynucleotide that has at least about 90%, preferably at least about 95% sequence identity with a polynucleotide encoding a polypeptide comprising the sequence of amino acids 1 to 839 of Figure 209 (SEQ ID NO:496); or at least about 90%, preferably at least about 95% sequence identity with a polynucleotide encoding a polypeptide comprising the sequence of amino acids 1 to 1041 of Figure 211 (SEQ ID NO:498).

In a specific embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding native or variant PRO285 and PRO286 polypeptides, with or without the N-terminal signal sequence, and with or without the transmembrane regions of the respective full-length sequences. In one aspect, the isolated nucleic acid comprises DNA encoding a mature, full-length native PRO285 or PRO286 polypeptide having amino acid residues 1 to 1049 of Figure 209 (SEQ ID NO:496) and 1 to 1041 of Figure 211 (SEQ ID NO: 498), or is complementary to such encoding nucleic acid sequence. In another aspect, the invention concerns an isolated nucleic acid molecule that comprises DNA encoding a native PRO285 or PRO286 polypeptide without an N-terminal signal sequence, or is complementary to such encoding nucleic acid sequence. In yet another embodiment, the invention concerns nucleic acid encoding transmembrane-domain deleted or inactivated forms of the full-length native PRO285 or PRO286 proteins.

In another embodiment, the invention the isolated nucleic acid molecule comprises the clone (DNA40021-1154) deposited on October 17, 1997, under ATCC number 209389; or the clone (DNA42663-1154) deposited on October 17, 1997, under ATCC number 209386.

In yet another embodiment, the invention provides a vector comprising DNA encoding PRO285 and PRO286 polypeptides, or their variants. Thus, the vector may comprise any of the isolated nucleic acid molecules hereinabove defined.

In another embodiment, the invention provides isolated PRO285 and PRO286 polypeptides. In particular, the invention provides isolated native sequence PRO285 and PRO286 polypeptides, which in one embodiment, include the amino acid sequences comprising residues 1 to 1049 and 1 to 1041 of Figures 209 and 211 (SEQ ID NOS:496 and 498), respectively. The invention also provides for variants of the PRO285 and PRO286 polypeptides which are encoded by any of the isolated nucleic acid molecules hereinabove defined. Specific variants include, but are not limited to, deletion (truncated) variants of the full-length native sequence PRO285 and PRO286 polypeptides which lack the respective N-terminal signal sequences and/or have their respective transmembrane and/or cytoplasmic domains deleted or inactivated.

The invention also specifically includes antibodies with dual specificities, e.g., bispecific antibodies binding more than one Toll polypeptide.

In yet another embodiment, the invention concerns agonists and antagonists of the native PRO285 and PRO286 polypeptides. In a particular embodiment, the agonist or antagonist is an anti-PRO285 or anti-PRO286 antibody.

5 In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of the native PRO285 and PRO286 polypeptides.

In a still further embodiment, the invention concerns a composition comprising a PRO285 or PRO286 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

10 The invention further concerns a composition comprising an antibody specifically binding a PRO285 or PRO286 polypeptide, in combination with a pharmaceutically acceptable carrier.

The invention also concerns a method of treating septic shock comprising administering to a patient an effective amount of an antagonist of a PRO285 or PRO286 polypeptide. In a specific embodiment, the antagonist is a blocking antibody specifically binding a native PRO285 or PRO286 polypeptide.

15

84. PRO213-1, PRO1330 and PRO1449

The present invention concerns compositions and methods for the diagnosis and treatment of neoplastic cell growth and proliferation in mammals, including humans. The present invention is based on the identification of genes that are amplified in the genome of tumor cells. Such gene amplification is expected to be associated with the 20 overexpression of the gene product and contribute to tumorigenesis. Accordingly, the proteins encoded by the amplified genes are believed to be useful targets for the diagnosis and/or treatment (including prevention) of certain cancers, and may act as predictors of the prognosis of tumor treatment.

In one embodiment, the present invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO213-1, PRO1330 and/or PRO1449 polypeptide. In one aspect, the isolated nucleic acid comprises DNA 25 encoding the PRO213-1, PRO1330 and/or PRO1449 polypeptide having amino acid residues 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) and 20 to 273 of Figure 217 (SEQ ID NO:510), respectively, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector designated as DNA30943-1163 (ATCC 209791) deposited on April 21, 1998; 30 DNA64907-1163-1 (ATCC 203242) deposited on September 9, 1998 and/or DNA64908-1163-1 (ATCC 203243) deposited on September 9, 1998.

In another embodiment, the present invention comprises an isolated nucleic acid molecule having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO213-1, 35 PRO1330 and/or PRO1449 polypeptide having amino acid residues 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) and 20 to 273 of Figure 217 (SEQ ID NO:510), respectively; or (b) the complement of the DNA molecule of (a).

In another embodiment, the invention provides an isolated PRO213-1, PRO1330 and/or PRO1449 polypeptide. In particular, the invention provides isolated native sequence PRO213-1, PRO1330 and/or PRO1449

polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) or 20 to 273 of Figure 217 (SEQ ID NO:510), respectively. Optionally, the PRO213-1, PRO1330 and/or PRO1449 polypeptide is obtained or obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA30943-1163 (ATCC 209791), DNA64907-1163-1 (ATCC 203242) or DNA64908-1163-1 (ATCC 203243).

5 In another aspect, the invention provides an isolated PRO213-1, PRO1330, and/or PRO1449 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 95% sequence identity to amino acid residues 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) or 20 to 273 of Figure 217 (SEQ ID NO:510), inclusive.

10 In yet another embodiment, the invention provides an isolated PRO213-1, PRO1330, and/or PRO1449 polypeptide, comprising the amino acid residues 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) or 20 to 273 of Figure 217 (SEQ ID NO:510), or a fragment thereof sufficient to provide a binding site for an anti-PRO213-1, anti-PRO1330 and/or anti-PRO1449 antibody. Preferably, the PRO213-1, PRO1330, and/or PRO1449 fragment retains a qualitative biological activity of a native PRO213-1, PRO1330, and/or PRO1449 polypeptide.

15 In a further aspect, the invention concerns an isolated PRO213-1, PRO1330, and/or PRO1449 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) and 20 to 273 of Figure 217 (SEQ ID NO:510), respectively.

20 In still a further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with: (a) a DNA molecule encoding a PRO213-1, PRO1330, and/or PRO1449 polypeptide having the amino acid residues from 1 to 295 of Figure 213 (SEQ ID NO:506), 20 to 273 of Figure 215 (SEQ ID NO:508) and 20 to 273 of Figure 217 (SEQ ID NO:510), respectively; or the complement of the DNA 25 molecule of (a), and if said test DNA molecule has at least about an 80% sequence identity to (a) or (b), (ii) culturing a host cell comprising said test DNA molecule under conditions suitable for the expression of said polypeptide, and (iii) recovering said polypeptide from the cell culture.

25 In one embodiment, the present invention concerns an isolated antibody which binds a PRO213-1, PRO1330 and/or PRO1449 polypeptide. In one aspect, the antibody induces death of a cell overexpressing a PRO213-1, PRO1330 and/or PRO1449 polypeptide. In another aspect, the antibody is a monoclonal antibody, which preferably has nonhuman complementarity determining region (CDR) residues and human framework region (FR) residues. The antibody may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a single-chain antibody, or an anti-idiotypic antibody.

30 In another embodiment, the invention concerns a composition comprising an antibody which binds a PRO213-1, PRO1330 and/or PRO1449 polypeptide in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition comprises a therapeutically effective amount of the antibody. In another aspect, the composition comprises a further active ingredient, which may, for example, be a further antibody or a cytotoxic or chemotherapeutic agent. Preferably, the composition is sterile.

In a further embodiment, the invention concerns nucleic acid encoding an anti-PRO213-1, anti-PRO1330 and/or anti-PRO1449 antibody, and vectors and recombinant host cells comprising such nucleic acid.

The invention further concerns antagonists and agonists of a PRO213-1, PRO1330 and/or PRO1449 polypeptide that inhibit one or more of the functions or activities of the PRO213-1, PRO1330 and/or PRO1449 polypeptide.

5 In a further embodiment, the invention concerns isolated nucleic acid molecules that hybridize to the complement of the nucleic acid molecules encoding the PRO213-1, PRO1330 and/or PRO1449 polypeptides. The nucleic acid preferably is DNA, and hybridization preferably occurs under stringent conditions. Such nucleic acid molecules can act as antisense molecules of the amplified genes identified herein, which, in turn, can find use in the modulation of the respective amplified genes, or as antisense primers in amplification reactions. Furthermore, such
10 sequences can be used as part of ribozyme and/or triple helix sequence which, in turn, may be used in regulation of the amplified genes.

15 In another embodiment, the invention concerns a method for determining the presence of a PRO213-1, PRO1330 and/or PRO1449 polypeptide comprising exposing a cell suspected of containing the PRO213-1, PRO1330 and/or PRO1449 polypeptide to an anti-PRO213-1, PRO1330 and/or PRO1449 antibody and determining binding of the antibody to the cell.

20 In yet another embodiment, the present invention concerns a method of diagnosing tumor in a mammal, comprising detecting the level of expression of a gene encoding a PRO213-1, PRO1330 and/or PRO1449 polypeptide (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher expression level in the test sample indicates the presence of tumor in the mammal from which the test tissue cells were obtained.

25 In another embodiment, the present invention concerns a method of diagnosing tumor in a mammal, comprising (a) contacting an anti-PRO213-1, anti-PRO1330 and/or anti-PRO1449 antibody with a test sample of tissue cells obtained from the mammal, and (b) detecting the formation of a complex between the anti-PRO213-1, anti-PRO1330 and/or anti-PRO1449 antibody and the PRO213-1, PRO1330 and/or PRO1449 polypeptide in the test sample. The detection may be qualitative or quantitative, and may be performed in comparison with monitoring the complex formation in a control sample of known normal tissue cells of the same cell type. A larger quantity of complexes formed in the test sample indicates the presence of tumor in the mammal from which the test tissue cells were obtained. The antibody preferably carries a detectable label. Complex formation can be monitored, for example, by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. The test sample
30 is usually obtained from an individual suspected to have neoplastic cell growth or proliferation (e.g. cancerous cells).

In another embodiment, the present invention concerns a cancer diagnostic kit, comprising an anti-PRO213-1, anti-PRO1330 and/or anti-PRO1449 antibody and a carrier (e.g. a buffer) in suitable packaging. The kit preferably contains instructions for using the antibody to detect the PRO213-1, PRO1330 and/or PRO1449 polypeptide.

35 In yet another embodiment, the invention concerns a method for inhibiting the growth of tumor cells comprising exposing a cell which overexpresses a PRO213-1, PRO1330 and/or PRO1449 polypeptide to an effective amount of an agent inhibiting the expression and/or activity of the PRO213-1, PRO1330 and/or PRO1449 polypeptide. The agent preferably is an anti-PRO213-1, anti-PRO1330 and/or anti-PRO1449 antibody, a small organic and inorganic molecule, peptide, phosphopeptide, antisense or ribozyme molecule, or a triple helix molecule. In a specific aspect, the agent, e.g. anti-PRO213-1, anti-PRO1330 and/or anti-PRO1449 antibody induces cell death.

In a further aspect, the tumor cells are further exposed to radiation treatment and/or a cytotoxic or chemotherapeutic agent.

In a further embodiment, the invention concerns an article of manufacture, comprising:

- a) a container;
- b) a label on the container; and
- 5 c) a composition comprising an active agent contained within the container; wherein the composition is effective for inhibiting the growth of tumor cells, the label on the container indicates that the composition can be used for treating conditions characterized by overexpression of a PRO213-1, PRO1330 and/or PRO1449 polypeptide, and the active agent in the composition is an agent inhibiting the expression and/or activity of the PRO213-1, PRO1330 and/or PRO1449 polypeptide. In a preferred aspect, the active agent is an anti-PRO213-1, anti-PRO1330 and/or anti-
10 PRO1449 antibody.

In yet a further embodiment, the invention provides a method for identifying a compound capable of inhibiting the expression and/or activity of a PRO213-1, PRO1330 and/or PRO1449 polypeptide, comprising contacting a candidate compound with a PRO213-1, PRO1330 and/or PRO1449 polypeptide under conditions and for a time sufficient to allow these two components to interact. In a specific aspect, either the candidate compound
15 or the PRO213-1, PRO1330 and/or PRO1449 polypeptide is immobilized on a solid support. In another aspect, the non-immobilized component carries a detectable label.

85. PRO298

Applicants have identified a cDNA clone that encodes a novel polypeptide. The DNA is designated in the
20 present application as "DNA39975-1210", encoding a novel multi-transmembrane protein, referred to as "PRO298".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA having at least about 80%, preferably at least about 85%, more preferably at least about 90%, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding PRO298, comprising the sequence of amino acids 1 to 364 of Figure 219 (SEQ ID NO:515), or (b) the complement of the DNA molecule of (a). In one aspect, the isolated nucleic
25 acid comprises DNA encoding a PRO298 polypeptide having amino acid residues 1 to 364 of Figure 219 (SEQ ID NO:515), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions.

In a further embodiment, the invention concerns an isolated nucleic acid molecule comprising DNA having at least an 80% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the
30 human protein cDNA in ATCC Deposit No. 209783 (DNA39975-1210), or (b) the complement of the DNA molecule of (a).

In a still further embodiment, the invention concerns nucleic acid which comprises a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209783 (DNA39975-1210).

35 In another embodiment, the invention provides isolated PRO298 polypeptide. In particular, the invention provides isolated native sequence PRO298 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 364 of Figure 219 (SEQ ID NO:515).

In another embodiment, the invention provides an expressed sequence tag (EST) designated DNA26832 comprising the nucleotide sequence of Figure 220 (SEQ ID NO:516).

86. PRO337

Applicants have identified a cDNA clone (DNA43316-1237) that encodes a novel polypeptide, designated in the present application as "PRO337".

In one embodiment, the invention provides an isolated nucleic acid molecule having at least about 80% sequence identity to (a) a DNA molecule encoding a PRO337 polypeptide comprising the sequence of amino acids

- 5 1 to 344 of Figure 222 (SEQ ID NO:523), or (b) the complement of the DNA molecule of (a). The sequence identity preferably is about 85%, more preferably about 90%, most preferably about 95%. In one aspect, the isolated nucleic acid has at least about 80%, preferably at least about 85%, more preferably at least about 90%, and most preferably at least about 95 (including 96, 97, 98 and 99%) sequence identity with a polypeptide having amino acid residues 1 to 344 of Figure 222 (SEQ ID NO:523). Preferably, the highest degree of sequence identity occurs within the
10 immunoglobulin and major histocompatibility domains (amino acids 113 to 130 of Figure 222, SEQ ID NO:523).

In a further embodiment, the isolated nucleic acid molecule comprises DNA encoding a neurotrimin polypeptide having amino acid residues 1 to 344 of Figure 222 (SEQ ID NO:523), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the invention provides a nucleic acid of the full length protein of clone

- 15 DNA43316-1237, deposited with the ATCC under accession number ATCC 209487, alternatively the coding sequence of clone DNA43316-1237, deposited under accession number ATCC 209487.

In yet another embodiment, the invention provides isolated PRO337 polypeptide. In particular, the invention provides isolated native sequence PRO337 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 344 of Figure 222 (SEQ ID NO:523). Native PRO337 polypeptides with or without the
20 native signal sequence (amino acids 1 to about 28 in Figure 222 (SEQ ID NO:523), and with or without the initiating methionine are specifically included. Alternatively, the invention provides a PRO337 polypeptide encoded by the nucleic acid deposited under accession number ATCC 209487.

In yet another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequences identified in Figure 223 as DNA42301 (SEQ ID NO:524).

25

87. PRO403

Applicants have identified a cDNA clone (DNA55800-1263) that encodes a novel polypeptide, designated in the present application as "PRO403".

In one embodiment, the invention provides an isolated nucleic acid molecule having at least about 80% sequence identity to (a) a DNA molecule encoding a PRO403 polypeptide comprising the sequence of amino acids

- 30 1 to 736 of Figure 225 (SEQ ID NO:526), or (b) the complement of the DNA molecule of (a). The sequence identity preferably is about 85%, more preferably about 90%, most preferably about 95%. In one aspect, the isolated nucleic acid has at least about 80%, preferably at least about 85%, more preferably at least about 90%, and most preferably at least about 95% sequence identity with a polypeptide having amino acid residues 1 to 736 of Figure 225 (SEQ ID
35 NO:526). Preferably, the highest degree of sequence identity occurs within: (1) the putative N-glycosylation sites (amino acid residues 132, 136, 177, 237, 282, 349, 505, 598 and 606; (2) Cys residues conserved with the Kell blood group protein family (amino acid residues 65, 70, 88 and 96) and the putative zinc binding motif (amino acid residues 570-579).

In a further embodiment, the isolated nucleic acid molecule comprises DNA encoding a PRO403 polypeptide having amino acid residues 1 to 736 of Figure 225 (SEQ ID NO:526), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the invention provides a nucleic acid of the full length protein of clone DNA55800-1263, deposited with the ATCC under accession number ATCC 209680, alternatively the coding sequence of clone 5 DNA55800-1263, deposited under accession number ATCC 209680.

In yet another embodiment, the invention provides isolated PRO403 polypeptide. In particular, the invention provides isolated native sequence PRO403 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 736 of Figure 225 (SEQ ID NO:526). Native PRO403 polypeptides with or the initiating methionine are specifically included. Alternatively, the invention provides a PRO403 polypeptide encoded by the 10 nucleic acid deposited under accession number ATCC 209680.

In yet another embodiment, the invention provides an expressed sequence tag (EST) and other sequence fragments comprising the nucleotide sequences identified herein as DNA34415 (Figures 226A-B; SEQ ID NO:527); DNA49830 (Figure 227 ; SEQ ID NO:528) and DNA49831 (Figure 228; SEQ ID NO:529).

15 88. **Additional Embodiments**

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the above or below described polypeptides. A host cell comprising any such vector is also provided. By way of example, the host cells may be CHO cells, *E. coli*, or yeast. A process for producing any of the above or below described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression 20 of the desired polypeptide and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides chimeric molecules comprising any of the above or below described polypeptides fused to a heterologous polypeptide or amino acid sequence. An example of such a chimeric molecule comprises any of the above or below described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

25 In another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody.

In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences, wherein those probes may be derived from any of the above or below described nucleotide sequences.

30

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) of a native sequence PRO213 cDNA, wherein SEQ ID NO:1 is a clone designated herein as "UNQ187" and/or "DNA30943-1163".

35 Figure 2 shows the amino acid sequence (SEQ ID NO:2) derived from the coding sequence of SEQ ID NO:1 shown in Figure 1.

Figure 3 shows a nucleotide sequence (SEQ ID NO:6) of a native sequence PRO274 cDNA, wherein SEQ ID NO:6 is a clone designated herein as "UNQ241" and/or "DNA39987-1184".

Figure 4 shows the amino acid sequence (SEQ ID NO:7) derived from the coding sequence of SEQ ID NO:6 shown in Figure 3.

Figure 5 shows an EST nucleotide sequence designated herein as DNA17873 (SEQ ID NO:8).

Figure 6 shows an EST nucleotide sequence designated herein as DNA36157 (SEQ ID NO:9).

Figure 7 shows an EST nucleotide sequence designated herein as DNA28929 (SEQ ID NO:10).

Figure 8 shows a nucleotide sequence (SEQ ID NO:18) of a native sequence PRO300 cDNA, wherein SEQ ID NO:18 is a clone designated herein as "UNQ263" and/or "DNA40625-1189".

5 Figure 9 shows the amino acid sequence (SEQ ID NO:19) derived from the coding sequence of SEQ ID NO:18 shown in Figure 8.

Figure 10 shows a nucleotide sequence (SEQ ID NO:27) of a native sequence PRO284 cDNA, wherein SEQ ID NO:27 is a clone designated herein as "UNQ247" and/or "DNA23318-1211".

10 Figure 11 shows the amino acid sequence (SEQ ID NO:28) derived from the coding sequence of SEQ ID NO:27 shown in Figure 10.

Figure 12 shows an EST nucleotide sequence designated herein as DNA12982 (SEQ ID NO:29).

Figure 13 shows an EST nucleotide sequence designated herein as DNA15886 (SEQ ID NO:30).

Figure 14 shows a nucleotide sequence (SEQ ID NO:35) of a native sequence PRO296 cDNA, wherein SEQ ID NO:35 is a clone designated herein as "UNQ260" and/or "DNA39979-1213".

15 Figure 15 shows the amino acid sequence (SEQ ID NO:36) derived from the coding sequence of SEQ ID NO:35 shown in Figure 14.

Figure 16 shows an EST nucleotide sequence designated herein as DNA23020 (SEQ ID NO:37).

Figure 17 shows an EST nucleotide sequence designated herein as DNA21971 (SEQ ID NO:38).

Figure 18 shows an EST nucleotide sequence designated herein as DNA29037 (SEQ ID NO:39).

20 Figure 19 shows a nucleotide sequence (SEQ ID NO:44) of a native sequence PRO329 cDNA, wherein SEQ ID NO:44 is a clone designated herein as "UNQ291" and/or "DNA40594-1233".

Figure 20 shows the amino acid sequence (SEQ ID NO:45) derived from the coding sequence of SEQ ID NO:44 shown in Figure 19.

25 Figure 21 shows a nucleotide sequence (SEQ ID NO:51) of a native sequence PRO362 cDNA, wherein SEQ ID NO:51 is a clone designated herein as "UNQ317" and/or "DNA45416-1251".

Figure 22 shows the amino acid sequence (SEQ ID NO:52) derived from the coding sequence of SEQ ID NO:51 shown in Figure 21.

Figure 23 shows a nucleotide sequence (SEQ ID NO:58) of a native sequence PRO363 cDNA, wherein SEQ ID NO:58 is a clone designated herein as "UNQ318" and/or "DNA45419-1252".

30 Figure 24 shows the amino acid sequence (SEQ ID NO:59) derived from the coding sequence of SEQ ID NO:58 shown in Figure 23.

Figure 25 shows a nucleotide sequence (SEQ ID NO:63) of a native sequence PRO868 cDNA, wherein SEQ ID NO:63 is a clone designated herein as "UNQ437" and/or "DNA52594-1270".

35 Figure 26 shows the amino acid sequence (SEQ ID NO:64) derived from the coding sequence of SEQ ID NO:63 shown in Figure 25.

Figure 27 shows a nucleotide sequence (SEQ ID NO:68) of a native sequence PRO382 cDNA, wherein SEQ ID NO:68 is a clone designated herein as "UNQ323" and/or "DNA45234-1277".

Figure 28 shows the amino acid sequence (SEQ ID NO:69) derived from the coding sequence of SEQ ID NO:68 shown in Figure 27.

Figure 29 shows a nucleotide sequence (SEQ ID NO:73) of a native sequence PRO545 cDNA, wherein SEQ ID NO:73 is a clone designated herein as "UNQ346" and/or "DNA49624-1279".

Figure 30 shows the amino acid sequence (SEQ ID NO:74) derived from the coding sequence of SEQ ID NO:73 shown in Figure 29.

Figure 31 shows an EST nucleotide sequence designated herein as DNA13217 (SEQ ID NO:75).

5 Figure 32 shows a nucleotide sequence (SEQ ID NO:84) of a native sequence PRO617 cDNA, wherein SEQ ID NO:84 is a clone designated herein as "UNQ353" and/or "DNA48309-1280".

Figure 33 shows the amino acid sequence (SEQ ID NO:85) derived from the coding sequence of SEQ ID NO:84 shown in Figure 32.

10 Figure 34 shows a nucleotide sequence (SEQ ID NO:89) of a native sequence PRO700 cDNA, wherein SEQ ID NO:89 is a clone designated herein as "UNQ364" and/or "DNA46776-1284".

Figure 35 shows the amino acid sequence (SEQ ID NO:90) derived from the coding sequence of SEQ ID NO:89 shown in Figure 34.

Figure 36 shows a nucleotide sequence (SEQ ID NO:96) of a native sequence PRO702 cDNA, wherein SEQ ID NO:96 is a clone designated herein as "UNQ366" and/or "DNA50980-1286".

15 Figure 37 shows the amino acid sequence (SEQ ID NO:97) derived from the coding sequence of SEQ ID NO:96 shown in Figure 36.

Figure 38 shows a nucleotide sequence (SEQ ID NO:101) of a native sequence PRO703 cDNA, wherein SEQ ID NO:101 is a clone designated herein as "UNQ367" and/or "DNA50913-1287".

20 Figure 39 shows the amino acid sequence (SEQ ID NO:102) derived from the coding sequence of SEQ ID NO:101 shown in Figure 38.

Figure 40 shows a nucleotide sequence (SEQ ID NO:108) of a native sequence PRO705 cDNA, wherein SEQ ID NO:108 is a clone designated herein as "UNQ369" and/or "DNA50914-1289".

Figure 41 shows the amino acid sequence (SEQ ID NO:109) derived from the coding sequence of SEQ ID NO:108 shown in Figure 40.

25 Figures 42A-B show a nucleotide sequence (SEQ ID NO:113) of a native sequence PRO708 cDNA, wherein SEQ ID NO:113 is a clone designated herein as "UNQ372" and/or "DNA48296-1292".

Figure 43 shows the amino acid sequence (SEQ ID NO:114) derived from the coding sequence of SEQ ID NO:113 shown in Figures 42A-B.

30 Figure 44 shows a nucleotide sequence (SEQ ID NO:118) of a native sequence PRO320 cDNA, wherein SEQ ID NO:118 is a clone designated herein as "UNQ281" and/or "DNA32284-1307".

Figure 45 shows the amino acid sequence (SEQ ID NO:119) derived from the coding sequence of SEQ ID NO:118 shown in Figure 44.

Figure 46 shows a nucleotide sequence (SEQ ID NO:123) of a native sequence PRO324 cDNA, wherein SEQ ID NO:123 is a clone designated herein as "UNQ285" and/or "DNA36343-1310".

35 Figure 47 shows the amino acid sequence (SEQ ID NO:124) derived from the coding sequence of SEQ ID NO:123 shown in Figure 46.

Figure 48 shows a nucleotide sequence (SEQ ID NO:131) of a native sequence PRO351 cDNA, wherein SEQ ID NO:131 is a clone designated herein as "UNQ308" and/or "DNA40571-1315".

Figure 49 shows the amino acid sequence (SEQ ID NO:132) derived from the coding sequence of SEQ ID NO:131 shown in Figure 48.

Figure 50 shows a nucleotide sequence (SEQ ID NO:136) of a native sequence PRO352 cDNA, wherein SEQ ID NO:136 is a clone designated herein as "UNQ309" and/or "DNA41386-1316".

Figure 51 shows the amino acid sequence (SEQ ID NO:137) derived from the coding sequence of SEQ ID NO:136 shown in Figure 50.

Figure 52 shows a nucleotide sequence (SEQ ID NO:144) of a native sequence PRO381 cDNA, wherein SEQ ID NO:144 is a clone designated herein as "UNQ322" and/or "DNA44194-1317".

Figure 53 shows the amino acid sequence (SEQ ID NO:145) derived from the coding sequence of SEQ ID NO:144 shown in Figure 52.

Figure 54 shows a nucleotide sequence (SEQ ID NO:149) of a native sequence PRO386 cDNA, wherein SEQ ID NO:149 is a clone designated herein as "UNQ326" and/or "DNA45415-1318".

Figure 55 shows the amino acid sequence (SEQ ID NO:150) derived from the coding sequence of SEQ ID NO:149 shown in Figure 54.

Figure 56 shows an EST nucleotide sequence designated herein as DNA23350 (SEQ ID NO:151).

Figure 57 shows an EST nucleotide sequence designated herein as DNA23536 (SEQ ID NO:152).

Figure 58 shows a nucleotide sequence (SEQ ID NO:156) of a native sequence PRO540 cDNA, wherein SEQ ID NO:156 is a clone designated herein as "UNQ341" and/or "DNA44189-1322".

Figure 59 shows the amino acid sequence (SEQ ID NO:157) derived from the coding sequence of SEQ ID NO:156 shown in Figure 58.

Figure 60 shows a nucleotide sequence (SEQ ID NO:161) of a native sequence PRO615 cDNA, wherein SEQ ID NO:161 is a clone designated herein as "UNQ352" and/or "DNA48304-1323".

Figure 61 shows the amino acid sequence (SEQ ID NO:162) derived from the coding sequence of SEQ ID NO:161 shown in Figure 60.

Figure 62 shows a nucleotide sequence (SEQ ID NO:168) of a native sequence PRO618 cDNA, wherein SEQ ID NO:168 is a clone designated herein as "UNQ354" and/or "DNA49152-1324".

Figure 63 shows the amino acid sequence (SEQ ID NO:169) derived from the coding sequence of SEQ ID NO:168 shown in Figure 62.

Figure 64 shows an EST nucleotide sequence designated herein as DNA35597 (SEQ ID NO:170).

Figure 65 shows a nucleotide sequence (SEQ ID NO:177) of a native sequence PRO719 cDNA, wherein SEQ ID NO:177 is a clone designated herein as "UNQ387" and/or "DNA49646-1327".

Figure 66 shows the amino acid sequence (SEQ ID NO:178) derived from the coding sequence of SEQ ID NO:177 shown in Figure 65.

Figure 67 shows a nucleotide sequence (SEQ ID NO:182) of a native sequence PRO724 cDNA, wherein SEQ ID NO:182 is a clone designated herein as "UNQ389" and/or "DNA49631-1328".

Figure 68 shows the amino acid sequence (SEQ ID NO:183) derived from the coding sequence of SEQ ID NO:182 shown in Figure 67.

Figure 69 shows a nucleotide sequence (SEQ ID NO:189) of a native sequence PRO772 cDNA, wherein SEQ ID NO:189 is a clone designated herein as "UNQ410" and/or "DNA49645-1347".

Figure 70 shows the amino acid sequence (SEQ ID NO:190) derived from the coding sequence of SEQ ID NO:189 shown in Figure 69.

Figure 71 shows an EST nucleotide sequence designated herein as DNA43509 (SEQ ID NO:191).

Figure 72 shows a nucleotide sequence (SEQ ID NO:195) of a native sequence PRO852 cDNA, wherein SEQ ID NO:195 is a clone designated herein as "UNQ418" and/or "DNA45493-1349".

5 Figure 73 shows the amino acid sequence (SEQ ID NO:196) derived from the coding sequence of SEQ ID NO:195 shown in Figure 72.

Figure 74 shows a nucleotide sequence (SEQ ID NO:205) of a native sequence PRO853 cDNA, wherein SEQ ID NO:205 is a clone designated herein as "UNQ419" and/or "DNA48227-1350".

10 Figure 75 shows the amino acid sequence (SEQ ID NO:206) derived from the coding sequence of SEQ ID NO:205 shown in Figure 74.

Figures 76A-B show a nucleotide sequence (SEQ ID NO:210) of a native sequence PRO860 cDNA, wherein SEQ ID NO:210 is a clone designated herein as "UNQ421" and/or "DNA41404-1352".

Figure 77 shows the amino acid sequence (SEQ ID NO:211) derived from the coding sequence of SEQ ID NO:210 shown in Figures 76A-B.

15 Figure 78 shows a nucleotide sequence (SEQ ID NO:215) of a native sequence PRO846 cDNA, wherein SEQ ID NO:215 is a clone designated herein as "UNQ422" and/or "DNA44196-1353".

Figure 79 shows the amino acid sequence (SEQ ID NO:216) derived from the coding sequence of SEQ ID NO:215 shown in Figure 78.

20 Figure 80 shows a nucleotide sequence (SEQ ID NO:220) of a native sequence PRO862 cDNA, wherein SEQ ID NO:220 is a clone designated herein as "UNQ424" and/or "DNA52187-1354".

Figure 81 shows the amino acid sequence (SEQ ID NO:221) derived from the coding sequence of SEQ ID NO:220 shown in Figure 80.

Figure 82 shows a nucleotide sequence (SEQ ID NO:225) of a native sequence PRO864 cDNA, wherein SEQ ID NO:225 is a clone designated herein as "UNQ426" and/or "DNA48328-1355".

25 Figure 83 shows the amino acid sequence (SEQ ID NO:226) derived from the coding sequence of SEQ ID NO:225 shown in Figure 82.

Figure 84 shows a nucleotide sequence (SEQ ID NO:230) of a native sequence PRO792 cDNA, wherein SEQ ID NO:230 is a clone designated herein as "UNQ431" and/or "DNA56352-1358".

30 Figure 85 shows the amino acid sequence (SEQ ID NO:231) derived from the coding sequence of SEQ ID NO:230 shown in Figure 84.

Figure 86 shows a nucleotide sequence (SEQ ID NO:235) of a native sequence PRO866 cDNA, wherein SEQ ID NO:235 is a clone designated herein as "UNQ435" and/or "DNA53971-1359".

Figure 87 shows the amino acid sequence (SEQ ID NO:236) derived from the coding sequence of SEQ ID NO:235 shown in Figure 86.

35 Figure 88 shows a nucleotide sequence (SEQ ID NO:244) of a native sequence PRO871 cDNA, wherein SEQ ID NO:244 is a clone designated herein as "UNQ438" and/or "DNA50919-1361".

Figure 89 shows the amino acid sequence (SEQ ID NO:245) derived from the coding sequence of SEQ ID NO:244 shown in Figure 88.

Figure 90 shows a nucleotide sequence (SEQ ID NO:253) of a native sequence PRO873 cDNA, wherein SEQ ID NO:253 is a clone designated herein as "UNQ440" and/or "DNA44179-1362".

Figure 91 shows the amino acid sequence (SEQ ID NO:254) derived from the coding sequence of SEQ ID NO:253 shown in Figure 90.

Figure 92 shows a nucleotide sequence (SEQ ID NO:258) of a native sequence PRO940 cDNA, wherein
5 SEQ ID NO:258 is a clone designated herein as "UNQ477" and/or "DNA54002-1367".

Figure 93 shows the amino acid sequence (SEQ ID NO:259) derived from the coding sequence of SEQ ID NO:258 shown in Figure 92.

Figure 94 shows a nucleotide sequence (SEQ ID NO:263) of a native sequence PRO941 cDNA, wherein SEQ ID NO:263 is a clone designated herein as "UNQ478" and/or "DNA53906-1368".

10 Figure 95 shows the amino acid sequence (SEQ ID NO:264) derived from the coding sequence of SEQ ID NO:263 shown in Figure 94.

Figure 96 shows an EST nucleotide sequence designated herein as DNA6415 (SEQ ID NO:265).

Figure 97 shows a nucleotide sequence (SEQ ID NO:269) of a native sequence PRO944 cDNA, wherein SEQ ID NO:269 is a clone designated herein as "UNQ481" and/or "DNA52185-1370".

15 Figure 98 shows the amino acid sequence (SEQ ID NO:270) derived from the coding sequence of SEQ ID NO:269 shown in Figure 97.

Figure 99 shows an EST nucleotide sequence designated herein as DNA14007 (SEQ ID NO:271).

Figure 100 shows an EST nucleotide sequence designated herein as DNA12773 (SEQ ID NO:272).

Figure 101 shows an EST nucleotide sequence designated herein as DNA12746 (SEQ ID NO:273).

20 Figure 102 shows an EST nucleotide sequence designated herein as DNA12834 (SEQ ID NO:274).

Figure 103 shows an EST nucleotide sequence designated herein as DNA12846 (SEQ ID NO:275).

Figure 104 shows an EST nucleotide sequence designated herein as DNA13104 (SEQ ID NO:276).

Figure 105 shows an EST nucleotide sequence designated herein as DNA13259 (SEQ ID NO:277).

Figure 106 shows an EST nucleotide sequence designated herein as DNA13959 (SEQ ID NO:278).

25 Figure 107 shows an EST nucleotide sequence designated herein as DNA13961 (SEQ ID NO:279).

Figure 108 shows a nucleotide sequence (SEQ ID NO:283) of a native sequence PRO983 cDNA, wherein SEQ ID NO:283 is a clone designated herein as "UNQ484" and/or "DNA53977-1371".

Figure 109 shows the amino acid sequence (SEQ ID NO:284) derived from the coding sequence of SEQ ID NO:283 shown in Figure 108.

30 Figure 110 shows an EST nucleotide sequence designated herein as DNA17130 (SEQ ID NO:285).

Figure 111 shows an EST nucleotide sequence designated herein as DNA23466 (SEQ ID NO:286).

Figure 112 shows an EST nucleotide sequence designated herein as DNA26818 (SEQ ID NO:287).

Figure 113 shows an EST nucleotide sequence designated herein as DNA37618 (SEQ ID NO:288).

Figure 114 shows an EST nucleotide sequence designated herein as DNA41732 (SEQ ID NO:289).

35 Figure 115 shows an EST nucleotide sequence designated herein as DNA45980 (SEQ ID NO:290).

Figure 116 shows an EST nucleotide sequence designated herein as DNA46372 (SEQ ID NO:291).

Figure 117 shows a nucleotide sequence (SEQ ID NO:295) of a native sequence PRO1057 cDNA, wherein SEQ ID NO:295 is a clone designated herein as "UNQ522" and/or "DNA57253-1382".

Figure 118 shows the amino acid sequence (SEQ ID NO:296) derived from the coding sequence of SEQ ID NO:295 shown in Figure 117.

Figure 119 shows a nucleotide sequence (SEQ ID NO:300) of a native sequence PRO1071 cDNA, wherein SEQ ID NO:300 is a clone designated herein as "UNQ528" and/or "DNA58847-1383".

Figure 120 shows the amino acid sequence (SEQ ID NO:301) derived from the coding sequence of SEQ ID NO:300 shown in Figure 119.

Figure 121 shows a nucleotide sequence (SEQ ID NO:302) of a native sequence PRO1072 cDNA, wherein SEQ ID NO:302 is a clone designated herein as "UNQ529" and/or "DNA58747-1384".

Figure 122 shows the amino acid sequence (SEQ ID NO:303) derived from the coding sequence of SEQ ID NO:302 shown in Figure 121.

Figure 123 shows an EST nucleotide sequence designated herein as DNA40210 (SEQ ID NO:304).

Figure 124 shows a nucleotide sequence (SEQ ID NO:308) of a native sequence PRO1075 cDNA, wherein SEQ ID NO:308 is a clone designated herein as "UNQ532" and/or "DNA57689-1385".

Figure 125 shows the amino acid sequence (SEQ ID NO:309) derived from the coding sequence of SEQ ID NO:308 shown in Figure 124.

Figure 126 shows an EST nucleotide sequence designated herein as DNA13059 (SEQ ID NO:310).

Figure 127 shows an EST nucleotide sequence designated herein as DNA19463 (SEQ ID NO:311).

Figure 128 shows a nucleotide sequence (SEQ ID NO:321) of a native sequence PRO181 cDNA, wherein SEQ ID NO:321 is a clone designated herein as "UNQ155" and/or "DNA23330-1390".

Figure 129 shows the amino acid sequence (SEQ ID NO:322) derived from the coding sequence of SEQ ID NO:321 shown in Figure 128.

Figure 130 shows an EST nucleotide sequence designated herein as DNA13242 (SEQ ID NO:323).

Figure 131 shows a nucleotide sequence (SEQ ID NO:329) of a native sequence PRO195 cDNA, wherein SEQ ID NO:329 is a clone designated herein as "UNQ169" and/or "DNA26847-1395".

Figure 132 shows the amino acid sequence (SEQ ID NO:330) derived from the coding sequence of SEQ ID NO:329 shown in Figure 131.

Figure 133 shows an EST nucleotide sequence designated herein as DNA15062 (SEQ ID NO:331).

Figure 134 shows an EST nucleotide sequence designated herein as DNA13199 (SEQ ID NO:332).

Figure 135 shows a nucleotide sequence (SEQ ID NO:336) of a native sequence PRO865 cDNA, wherein SEQ ID NO:336 is a clone designated herein as "UNQ434" and/or "DNA53974-1401".

Figure 136 shows the amino acid sequence (SEQ ID NO:337) derived from the coding sequence of SEQ ID NO:336 shown in Figure 135.

Figure 137 shows an EST nucleotide sequence designated herein as DNA37642 (SEQ ID NO:338).

Figure 138 shows a nucleotide sequence (SEQ ID NO:345) of a native sequence PRO827 cDNA, wherein SEQ ID NO:345 is a clone designated herein as "UNQ468" and/or "DNA57039-1402".

Figure 139 shows the amino acid sequence (SEQ ID NO:346) derived from the coding sequence of SEQ ID NO:345 shown in Figure 138.

Figure 140 shows an EST nucleotide sequence designated herein as DNA47751 (SEQ ID NO:347).

Figure 141 shows a nucleotide sequence (SEQ ID NO:351) of a native sequence PRO1114 cDNA, wherein SEQ ID NO:351 is a clone designated herein as "UNQ557" and/or "DNA57033-1403".

Figure 142 shows the amino acid sequence (SEQ ID NO:352) derived from the coding sequence of SEQ ID NO:351 shown in Figure 141.

Figure 143 shows an EST nucleotide sequence designated herein as DNA48466 (SEQ ID NO:353).

Figure 144 shows a nucleotide sequence (SEQ ID NO:357) of a native sequence PRO237 cDNA, wherein SEQ ID NO:357 is a clone designated herein as "UNQ211" and/or "DNA34353-1428".

5 Figure 145 shows the amino acid sequence (SEQ ID NO:358) derived from the coding sequence of SEQ ID NO:357 shown in Figure 144.

Figure 146 shows a nucleotide sequence (SEQ ID NO:362) of a native sequence PRO541 cDNA, wherein SEQ ID NO:362 is a clone designated herein as "UNQ342" and/or "DNA45417-1432".

10 Figure 147 shows the amino acid sequence (SEQ ID NO:363) derived from the coding sequence of SEQ ID NO:362 shown in Figure 146.

Figure 148 shows a nucleotide sequence (SEQ ID NO:369) of a native sequence PRO273 cDNA, wherein SEQ ID NO:369 is a clone designated herein as "UNQ240" and/or "DNA39523-1192".

Figure 149 shows the amino acid sequence (SEQ ID NO:370) derived from the coding sequence of SEQ ID NO:369 shown in Figure 148.

15 Figure 150 shows a nucleotide sequence (SEQ ID NO:374) of a native sequence PRO701 cDNA, wherein SEQ ID NO:374 is a clone designated herein as "UNQ365" and/or "DNA44205-1285".

Figure 151 shows the amino acid sequence (SEQ ID NO:375) derived from the coding sequence of SEQ ID NO:374 shown in Figure 150.

20 Figure 152 shows a nucleotide sequence (SEQ ID NO:379) of a native sequence PRO704 cDNA, wherein SEQ ID NO:379 is a clone designated herein as "UNQ368" and/or "DNA50911-1288".

Figure 153 shows the amino acid sequence (SEQ ID NO:380) derived from the coding sequence of SEQ ID NO:379 shown in Figure 152.

Figure 154 shows a nucleotide sequence (SEQ ID NO:384) of a native sequence PRO706 cDNA, wherein SEQ ID NO:384 is a clone designated herein as "UNQ370" and/or "DNA48329-1290".

25 Figure 155 shows the amino acid sequence (SEQ ID NO:385) derived from the coding sequence of SEQ ID NO:384 shown in Figure 154.

Figure 156 shows a nucleotide sequence (SEQ ID NO:389) of a native sequence PRO707 cDNA, wherein SEQ ID NO:389 is a clone designated herein as "UNQ371" and/or "DNA48306-1291".

30 Figure 157 shows the amino acid sequence (SEQ ID NO:390) derived from the coding sequence of SEQ ID NO:389 shown in Figure 156.

Figure 158 shows a nucleotide sequence (SEQ ID NO:394) of a native sequence PRO322 cDNA, wherein SEQ ID NO:394 is a clone designated herein as "UNQ283" and/or "DNA48336-1309".

Figure 159 shows the amino acid sequence (SEQ ID NO:395) derived from the coding sequence of SEQ ID NO:394 shown in Figure 158.

35 Figure 160 shows a nucleotide sequence (SEQ ID NO:399) of a native sequence PRO526 cDNA, wherein SEQ ID NO:399 is a clone designated herein as "UNQ330" and/or "DNA44184-1319".

Figure 161 shows the amino acid sequence (SEQ ID NO:400) derived from the coding sequence of SEQ ID NO:399 shown in Figure 160.

Figure 162 shows a nucleotide sequence (SEQ ID NO:404) of a native sequence PRO531 cDNA, wherein SEQ ID NO:404 is a clone designated herein as "UNQ332" and/or "DNA48314-1320".

Figure 163 shows the amino acid sequence (SEQ ID NO:405) derived from the coding sequence of SEQ ID NO:404 shown in Figure 162.

Figure 164 shows a nucleotide sequence (SEQ ID NO:409) of a native sequence PRO534 cDNA, wherein 5 SEQ ID NO:409 is a clone designated herein as "UNQ335" and/or "DNA48333-1321".

Figure 165 shows the amino acid sequence (SEQ ID NO:410) derived from the coding sequence of SEQ ID NO:409 shown in Figure 164.

Figure 166 shows a nucleotide sequence (SEQ ID NO:414) of a native sequence PRO697 cDNA, wherein SEQ ID NO:414 is a clone designated herein as "UNQ361" and/or "DNA50920-1325".

10 Figure 167 shows the amino acid sequence (SEQ ID NO:415) derived from the coding sequence of SEQ ID NO:414 shown in Figure 166.

Figure 168 shows a nucleotide sequence (SEQ ID NO:419) of a native sequence PRO717 cDNA, wherein SEQ ID NO:419 is a clone designated herein as "UNQ385" and/or "DNA50988-1326".

15 Figure 169 shows the amino acid sequence (SEQ ID NO:420) derived from the coding sequence of SEQ ID NO:419 shown in Figure 168.

Figures 170A-B show a nucleotide sequence (SEQ ID NO:424) of a native sequence PRO731 cDNA, wherein SEQ ID NO:424 is a clone designated herein as "UNQ395" and/or "DNA48331-1329".

Figure 171 shows the amino acid sequence (SEQ ID NO:425) derived from the coding sequence of SEQ ID NO:424 shown in Figures 170A-B.

20 Figure 172 shows a nucleotide sequence (SEQ ID NO:429) of a native sequence PRO218 cDNA, wherein SEQ ID NO:429 is a clone designated herein as "UNQ192" and/or "DNA30867-1335".

Figure 173 shows the amino acid sequence (SEQ ID NO:430) derived from the coding sequence of SEQ ID NO:429 shown in Figure 172.

Figure 174 shows an EST nucleotide sequence designated herein as DNA14472 (SEQ ID NO:431).

25 Figure 175 shows an EST nucleotide sequence designated herein as DNA15846 (SEQ ID NO:432).

Figures 176A-B show a nucleotide sequence (SEQ ID NO:436) of a native sequence PRO768 cDNA, wherein SEQ ID NO:436 is a clone designated herein as "UNQ406" and/or "DNA55737-1345".

Figure 177 shows the amino acid sequence (SEQ ID NO:437) derived from the coding sequence of SEQ ID NO:436 shown in Figures 176A-B.

30 Figure 178 shows a nucleotide sequence (SEQ ID NO:441) of a native sequence PRO771 cDNA, wherein SEQ ID NO:441 is a clone designated herein as "UNQ409" and/or "DNA49829-1346".

Figure 179 shows the amino acid sequence (SEQ ID NO:442) derived from the coding sequence of SEQ ID NO:441 shown in Figure 178.

Figures 180A-B show a nucleotide sequence (SEQ ID NO:446) of a native sequence PRO733 cDNA, 35 wherein SEQ ID NO:446 is a clone designated herein as "UNQ411" and/or "DNA52196-1348".

Figure 181 shows the amino acid sequence (SEQ ID NO:447) derived from the coding sequence of SEQ ID NO:446 shown in Figures 180A-B.

Figure 182 shows a nucleotide sequence (SEQ ID NO:451) of a native sequence PRO162 cDNA, wherein SEQ ID NO:451 is a clone designated herein as "UNQ429" and/or "DNA46965-1356".

Figure 183 shows the amino acid sequence (SEQ ID NO:452) derived from the coding sequence of SEQ ID NO:451 shown in Figure 182.

Figure 184 shows a nucleotide sequence (SEQ ID NO:453) of a native sequence PRO788 cDNA, wherein SEQ ID NO:453 is a clone designated herein as "UNQ430" and/or "DNA56405-1357".

Figure 185 shows the amino acid sequence (SEQ ID NO:454) derived from the coding sequence of SEQ ID NO:453 shown in Figure 184.

Figure 186 shows a nucleotide sequence (SEQ ID NO:455) of a native sequence PRO1008 cDNA, wherein SEQ ID NO:455 is a clone designated herein as "UNQ492" and/or "DNA57530-1375".

Figure 187 shows the amino acid sequence (SEQ ID NO:456) derived from the coding sequence of SEQ ID NO:455 shown in Figure 186.

10 Figure 188 shows an EST nucleotide sequence designated herein as DNA16508 (SEQ ID NO:457).

Figures 189A-B show a nucleotide sequence (SEQ ID NO:458) of a native sequence PRO1012 cDNA, wherein SEQ ID NO:458 is a clone designated herein as "UNQ495" and/or "DNA56439-1376".

Figure 190 shows the amino acid sequence (SEQ ID NO:459) derived from the coding sequence of SEQ ID NO:458 shown in Figures 189A-B.

15 Figure 191 shows a nucleotide sequence (SEQ ID NO:463) of a native sequence PRO1014 cDNA, wherein SEQ ID NO:463 is a clone designated herein as "UNQ497" and/or "DNA56409-1377".

Figure 192 shows the amino acid sequence (SEQ ID NO:464) derived from the coding sequence of SEQ ID NO:463 shown in Figure 191.

20 Figure 193 shows a nucleotide sequence (SEQ ID NO:465) of a native sequence PRO1017 cDNA, wherein SEQ ID NO:465 is a clone designated herein as "UNQ500" and/or "DNA56112-1379".

Figure 194 shows the amino acid sequence (SEQ ID NO:466) derived from the coding sequence of SEQ ID NO:465 shown in Figure 193.

Figure 195 shows a nucleotide sequence (SEQ ID NO:467) of a native sequence PRO474 cDNA, wherein SEQ ID NO:467 is a clone designated herein as "UNQ502" and/or "DNA56045-1380".

25 Figure 196 shows the amino acid sequence (SEQ ID NO:468) derived from the coding sequence of SEQ ID NO:467 shown in Figure 195.

Figure 197 shows a nucleotide sequence (SEQ ID NO:469) of a native sequence PRO1031 cDNA, wherein SEQ ID NO:469 is a clone designated herein as "UNQ516" and/or "DNA59294-1381".

30 Figure 198 shows the amino acid sequence (SEQ ID NO:470) derived from the coding sequence of SEQ ID NO:469 shown in Figure 197.

Figure 199 shows a nucleotide sequence (SEQ ID NO:471) of a native sequence PRO938 cDNA, wherein SEQ ID NO:471 is a clone designated herein as "UNQ475" and/or "DNA56433-1406".

Figure 200 shows the amino acid sequence (SEQ ID NO:472) derived from the coding sequence of SEQ ID NO:471 shown in Figure 199.

35 Figure 201 shows a nucleotide sequence (SEQ ID NO:476) of a native sequence PRO1082 cDNA, wherein SEQ ID NO:476 is a clone designated herein as "UNQ539" and/or "DNA53912-1457".

Figure 202 shows the amino acid sequence (SEQ ID NO:477) derived from the coding sequence of SEQ ID NO:476 shown in Figure 201.

Figure 203 shows a nucleotide sequence (SEQ ID NO:482) of a native sequence PRO1083 cDNA, wherein SEQ ID NO:482 is a clone designated herein as "UNQ540" and/or "DNA50921-1458".

Figure 204 shows the amino acid sequence (SEQ ID NO:483) derived from the coding sequence of SEQ ID NO:482 shown in Figure 203.

Figure 205 shows an EST nucleotide sequence designated herein as DNA24256 (SEQ ID NO:484).

5 Figure 206 shows a nucleotide sequence (SEQ ID NO:487) of a native sequence PRO200 cDNA, wherein SEQ ID NO:487 is a clone designated herein as "UNQ174" and/or "DNA29101-1122".

Figure 207 shows the amino acid sequence (SEQ ID NO:488) derived from the coding sequence of SEQ ID NO:487 shown in Figure 206.

10 Figure 208 shows a nucleotide sequence (SEQ ID NO:495) of a native sequence PRO285 cDNA, wherein SEQ ID NO:495 is a clone designated herein as "DNA40021-1154".

Figure 209 shows the amino acid sequence (SEQ ID NO:496) derived from the coding sequence of SEQ ID NO:495 shown in Figure 208.

Figures 210A-B show a nucleotide sequence (SEQ ID NO:497) of a native sequence PRO286 cDNA, wherein SEQ ID NO:497 is a clone designated herein as "DNA42663-1154".

15 Figure 211 shows the amino acid sequence (SEQ ID NO:498) derived from the coding sequence of SEQ ID NO:497 shown in Figures 210A-B.

Figure 212 shows a nucleotide sequence (SEQ ID NO:505) of a native sequence PRO213-1 cDNA, wherein SEQ ID NO:505 is a clone designated herein as "DNA30943-1-1163-1".

20 Figure 213 shows the amino acid sequence (SEQ ID NO:506) derived from the coding sequence of SEQ ID NO:505 shown in Figure 212.

Figure 214 shows a nucleotide sequence (SEQ ID NO:507) of a native sequence PRO1330 cDNA, wherein SEQ ID NO:507 is a clone designated herein as "DNA64907-1163-1".

Figure 215 shows the amino acid sequence (SEQ ID NO:508) derived from the coding sequence of SEQ ID NO:507 shown in Figure 214.

25 Figure 216 shows a nucleotide sequence (SEQ ID NO:509) of a native sequence PRO1449 cDNA, wherein SEQ ID NO:509 is a clone designated herein as "DNA64908-1163-1".

Figure 217 shows the amino acid sequence (SEQ ID NO:510) derived from the coding sequence of SEQ ID NO:509 shown in Figure 216.

30 Figure 218 shows a nucleotide sequence (SEQ ID NO:514) of a native sequence PRO298 cDNA, wherein SEQ ID NO:514 is a clone designated herein as "UNQ261" and/or "DNA39975-1210".

Figure 219 shows the amino acid sequence (SEQ ID NO:515) derived from the coding sequence of SEQ ID NO:514 shown in Figure 218.

Figure 220 shows an EST nucleotide sequence designated herein as DNA26832 (SEQ ID NO:516).

35 Figure 221 shows a nucleotide sequence (SEQ ID NO:522) of a native sequence PRO337 cDNA, wherein SEQ ID NO:522 is a clone designated herein as "DNA43316-1237".

Figure 222 shows the amino acid sequence (SEQ ID NO:523) derived from the coding sequence of SEQ ID NO:522 shown in Figure 221.

Figure 223 shows an EST nucleotide sequence designated herein as DNA42301 (SEQ ID NO:524).

Figure 224 shows a nucleotide sequence (SEQ ID NO:525) of a native sequence PRO403 cDNA, wherein SEQ ID NO:525 is a clone designated herein as "DNA55800-1263".

Figure 225 shows the amino acid sequence (SEQ ID NO:526) derived from the coding sequence of SEQ ID NO:525 shown in Figure 224.

Figures 226A-B show an EST nucleotide sequence designated herein as DNA34415 (SEQ ID NO:527).

5 Figure 227 shows an EST nucleotide sequence designated herein as DNA49830 (SEQ ID NO:528).

Figure 228 shows an EST nucleotide sequence designated herein as DNA49831 (SEQ ID NO:529).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Definitions

10 The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i.e., PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from 15 another source, or prepared by recombinant or synthetic methods.

A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (e.g., an 20 extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO213 polypeptide is a mature or full-length native sequence PRO213 polypeptide comprising amino acids 1 to 295 of Figure 2 (SEQ ID NO:2), the native sequence PRO274 polypeptide is a mature or full-length native sequence PRO274 polypeptide comprising amino acids 1 to 492 of Figure 4 (SEQ ID NO:7), the native sequence PRO300 polypeptide 25 is a mature or full-length native sequence PRO300 polypeptide comprising amino acids 1 to 457 of Figure 9 (SEQ ID NO:19), the native sequence PRO284 polypeptide is a mature or full-length native sequence PRO284 polypeptide comprising amino acids 1 to 285 of Figure 11 (SEQ ID NO:28), the native sequence PRO296 polypeptide is a mature or full-length native sequence PRO296 polypeptide comprising amino acids 1 to 204 of Figure 15 (SEQ ID NO:36), the native sequence PRO329 polypeptide is a mature or full-length native sequence PRO329 polypeptide comprising 30 amino acids 1 to 359 of Figure 20 (SEQ ID NO:45), the native sequence PRO362 polypeptide is a mature or full-length native sequence PRO362 polypeptide comprising amino acids 1 to 321 of Figure 22 (SEQ ID NO:52), the native sequence PRO363 polypeptide is a mature or full-length native sequence PRO363 polypeptide comprising amino acids 1 to 373 of Figure 24 (SEQ ID NO:59), the native sequence PRO868 polypeptide is a mature or full-length native sequence PRO868 polypeptide comprising amino acids 1 to 655 of Figure 26 (SEQ ID NO:64), the 35 native sequence PRO382 polypeptide is a mature or full-length native sequence PRO382 polypeptide comprising amino acids 1 to 453 of Figure 28 (SEQ ID NO:69), the native sequence PRO545 polypeptide is a mature or full-length native sequence PRO545 polypeptide comprising amino acids 1 to 735 of Figure 30 (SEQ ID NO:74), the native sequence PRO617 polypeptide is a mature or full-length native sequence PRO617 polypeptide comprising amino acids 1 to 67 of Figure 33 (SEQ ID NO:85), the native sequence PRO700 polypeptide is a mature or full-length

native sequence PRO700 polypeptide comprising amino acids 1 to 432 of Figure 35 (SEQ ID NO:90), the native sequence PRO702 polypeptide is a mature or full-length native sequence PRO702 polypeptide comprising amino acids 1 to 277 of Figure 37 (SEQ ID NO:97), the native sequence PRO703 polypeptide is a mature or full-length native sequence PRO703 polypeptide comprising amino acids 1 to 730 of Figure 39 (SEQ ID NO:102), the native sequence PRO705 polypeptide is a mature or full-length native sequence PRO705 polypeptide comprising amino acids 1 to 555
5 of Figure 41 (SEQ ID NO:109), the native sequence PRO708 polypeptide is a mature or full-length native sequence PRO708 polypeptide comprising amino acids 1 to 515 of Figure 43 (SEQ ID NO:114), the native sequence PRO320 polypeptide is a mature or full-length native sequence PRO320 polypeptide comprising amino acids 1 to 338 of Figure 45 (SEQ ID NO:119), the native sequence PRO324 polypeptide is a mature or full-length native sequence PRO324 polypeptide comprising amino acids 1 to 289 of Figure 47 (SEQ ID NO:124), the native sequence PRO351
10 polypeptide is a mature or full-length native sequence PRO351 polypeptide comprising amino acids 1 to 571 of Figure 49 (SEQ ID NO:132), the native sequence PRO352 polypeptide is a mature or full-length native sequence PRO352 polypeptide comprising amino acids 1 to 316 of Figure 51 (SEQ ID NO:137), the native sequence PRO381 polypeptide is a mature or full-length native sequence PRO381 polypeptide comprising amino acids 1 to 211 of Figure 53 (SEQ ID NO:145), the native sequence PRO386 polypeptide is a mature or full-length native sequence PRO386
15 polypeptide comprising amino acids 1 to 215 of Figure 55 (SEQ ID NO:150), the native sequence PRO540 polypeptide is a mature or full-length native sequence PRO540 polypeptide comprising amino acids 1 to 412 of Figure 59 (SEQ ID NO:157), the native sequence PRO615 polypeptide is a mature or full-length native sequence PRO615 polypeptide comprising amino acids 1 to 224 of Figure 61 (SEQ ID NO:162), the native sequence PRO618 polypeptide is a mature or full-length native sequence PRO618 polypeptide comprising amino acids 1 to 802 of Figure
20 63 (SEQ ID NO:169), the native sequence PRO719 polypeptide is a mature or full-length native sequence PRO719 polypeptide comprising amino acids 1 to 354 of Figure 66 (SEQ ID NO:178), the native sequence PRO724 polypeptide is a mature or full-length native sequence PRO724 polypeptide comprising amino acids 1 to 713 of Figure 68 (SEQ ID NO:183), the native sequence PRO772 polypeptide is a mature or full-length native sequence PRO772 polypeptide comprising amino acids 1 to 152 of Figure 70 (SEQ ID NO:190), the native sequence PRO852
25 polypeptide is a mature or full-length native sequence PRO852 polypeptide comprising amino acids 1 to 518 of Figure 73 (SEQ ID NO:196), the native sequence PRO853 polypeptide is a mature or full-length native sequence PRO853 polypeptide comprising amino acids 1 to 377 of Figure 75 (SEQ ID NO:206), the native sequence PRO860 polypeptide is a mature or full-length native sequence PRO860 polypeptide comprising amino acids 1 to 985 of Figure 77 (SEQ ID NO:211), the native sequence PRO846 polypeptide is a mature or full-length native sequence PRO846
30 polypeptide comprising amino acids 1 to 332 of Figure 79 (SEQ ID NO:216), the native sequence PRO862 polypeptide is a mature or full-length native sequence PRO862 polypeptide comprising amino acids 1 to 146 of Figure 81 (SEQ ID NO:221), the native sequence PRO864 polypeptide is a mature or full-length native sequence PRO864 polypeptide comprising amino acids 1 to 351 of Figure 83 (SEQ ID NO:226), the native sequence PRO792 polypeptide is a mature or full-length native sequence PRO792 polypeptide comprising amino acids 1 to 293 of Figure
35 85 (SEQ ID NO:231), the native sequence PRO866 polypeptide is a mature or full-length native sequence PRO866 polypeptide comprising amino acids 1 to 331 of Figure 87 (SEQ ID NO:236), the native sequence PRO871 polypeptide is a mature or full-length native sequence PRO871 polypeptide comprising amino acids 1 to 472 of Figure 89 (SEQ ID NO:245), the native sequence PRO873 polypeptide is a mature or full-length native sequence PRO873 polypeptide comprising amino acids 1 to 545 of Figure 91 (SEQ ID NO:254), the native sequence PRO940

polypeptide is a mature or full-length native sequence PRO940 polypeptide comprising amino acids 1 to 544 of Figure 93 (SEQ ID NO:259), the native sequence PRO941 polypeptide is a mature or full-length native sequence PRO941 polypeptide comprising amino acids 1 to 772 of Figure 95 (SEQ ID NO:264), the native sequence PRO944 polypeptide is a mature or full-length native sequence PRO944 polypeptide comprising amino acids 1 to 211 of Figure 98 (SEQ ID NO:270), the native sequence PRO983 polypeptide is a mature or full-length native sequence PRO983
5 polypeptide comprising amino acids 1 to 243 of Figure 109 (SEQ ID NO:284), the native sequence PRO1057 polypeptide is a mature or full-length native sequence PRO1057 polypeptide comprising amino acids 1 to 413 of Figure 118 (SEQ ID NO:296), the native sequence PRO1071 polypeptide is a mature or full-length native sequence PRO1071 polypeptide comprising amino acids 1 to 525 of Figure 120 (SEQ ID NO:301), the native sequence PRO1072 polypeptide is a mature or full-length native sequence PRO1072 polypeptide comprising amino acids 1 to
10 336 of Figure 122 (SEQ ID NO:303), the native sequence PRO1075 polypeptide is a mature or full-length native sequence PRO1075 polypeptide comprising amino acids 1 to 406 of Figure 125 (SEQ ID NO:309), the native sequence PRO181 polypeptide is a mature or full-length native sequence PRO181 polypeptide comprising amino acids 1 to 144 of Figure 129 (SEQ ID NO:322), the native sequence PRO195 polypeptide is a mature or full-length native sequence PRO195 polypeptide comprising amino acids 1 to 323 of Figure 132 (SEQ ID NO:330), the native sequence
15 PRO865 polypeptide is a mature or full-length native sequence PRO865 polypeptide comprising amino acids 1 to 468 of Figure 136 (SEQ ID NO:337), the native sequence PRO827 polypeptide is a mature or full-length native sequence PRO827 polypeptide comprising amino acids 1 to 124 of Figure 39 (SEQ ID NO:346), the native sequence PRO1114 polypeptide is a mature or full-length native sequence PRO1114 polypeptide comprising amino acids 1 to 311 of Figure 142 (SEQ ID NO:352), the native sequence PRO237 polypeptide is a mature or full-length native sequence
20 PRO237 polypeptide comprising amino acids 1 to 328 of Figure 145 (SEQ ID NO:358), the native sequence PRO541 polypeptide is a mature or full-length native sequence PRO541 polypeptide comprising amino acids 1 to 500 of Figure 147 (SEQ ID NO:363), the native sequence PRO273 polypeptide is a mature or full-length native sequence PRO273 polypeptide comprising amino acids 1 through 111 of Figure 149 (SEQ ID NO:370), the native sequence PRO701 polypeptide is a mature or full-length native sequence PRO701 polypeptide comprising amino acids 1 to 816 of Figure
25 151 (SEQ ID NO:375), the native sequence PRO704 polypeptide is a full-length or mature native sequence PRO704 polypeptide comprising amino acids 1 or 40 through 348 of Figure 153 (SEQ ID NO:380), the native sequence PRO706 polypeptide is a mature or full-length native sequence PRO706 polypeptide comprising amino acids 1 to 480 of Figure 155 (SEQ ID NO:385), the native sequence PRO707 polypeptide is a full-length or mature native sequence PRO707 polypeptide comprising amino acids 1 or 31 through 916 of Figure 157 (SEQ ID NO:390), the native
30 sequence PRO322 polypeptide is a mature or full-length native sequence PRO322 polypeptide comprising amino acids 24 or 1 to 260 of Figure 159 (SEQ ID NO:395), the native sequence PRO526 polypeptide is a full-length or mature native sequence PRO526 polypeptide comprising amino acids 1 or 27 through 473 of Figure 161 (SEQ ID NO:400), the native sequence PRO531 polypeptide is a mature PRO531 polypeptide comprising amino acids 1 to 789 of Figure 163 (SEQ ID NO:405), the native sequence PRO534 polypeptide is a mature or full-length native sequence PRO534
35 polypeptide comprising amino acids 1 to 360 of Figure 165 (SEQ ID NO:410), the native sequence PRO697 polypeptide is a full-length or mature native sequence PRO697 polypeptide comprising amino acids 1 or 21 through 295 of Figure 167 (SEQ ID NO:415), the native sequence PRO717 polypeptide is a mature or full-length native sequence PRO717 polypeptide comprising amino acids 1 through 560 of Figure 169 (SEQ ID NO:420), the native sequence PRO731 polypeptide is a full-length or mature native sequence PRO731 polypeptide comprising amino acids

1 or 14 through 1184 of Figure 171 (SEQ ID NO:425), the native sequence PRO218 polypeptide is a full-length or mature native sequence PRO218 polypeptide comprising amino acids 1 or 24 through 455 of Figure 173 (SEQ ID NO:430), the native sequence PRO768 polypeptide is a full-length or mature native sequence PRO768 polypeptide comprising amino acids 1 or 34 through 1141 of Figure 177 (SEQ ID NO:437), the native sequence PRO771 polypeptide is a full-length or mature native sequence PRO771 polypeptide comprising amino acids 1 or 17 through 5 436 of Figure 179 (SEQ ID NO:442), the native sequence PRO733 polypeptide is a mature or full-length native sequence PRO733 polypeptide comprising amino acids 24 or 1 through 229 of Figure 181 (SEQ ID NO:447), the native sequence PRO162 polypeptide is a full-length or mature native sequence PRO162 polypeptide comprising amino acids 1 or 27 through 175 of Figure 183 (SEQ ID NO:452), the native sequence PRO788 polypeptide is a full-length or mature native sequence PRO788 polypeptide comprising amino acids 1 or 18 through 125 of Figure 185 10 (SEQ ID NO:454), the native sequence PRO1008 polypeptide is a full-length or mature native sequence PRO1008 polypeptide comprising amino acids 1 or 24 through 266 of Figure 187 (SEQ ID NO:456), the native sequence PRO1012 polypeptide is a mature or full-length native sequence PRO1012 polypeptide comprising amino acids 1 through 747 of Figure 190 (SEQ ID NO:459), the native sequence PRO1014 polypeptide is a full-length or mature native sequence PRO1014 polypeptide comprising amino acids 1 or 20 through 300 of Figure 192 (SEQ ID NO:464), 15 the native sequence PRO1017 polypeptide is a full-length or mature native sequence PRO1017 polypeptide comprising amino acids 1 or 32 through 414 of Figure 194 (SEQ ID NO:466), the native sequence PRO474 polypeptide is a mature or full-length native sequence PRO474 polypeptide comprising amino acids 1 through 270 of Figure 196 (SEQ ID NO:468), the native sequence PRO1031 polypeptide is a full-length or mature native sequence PRO1031 polypeptide comprising amino acids 1 or 21 through 180 of Figure 198 (SEQ ID NO:470), the native sequence 20 PRO938 polypeptide is a mature or full-length native sequence PRO938 polypeptide comprising amino acids 1 to 349 of Figure 200 (SEQ ID NO:472), the native sequence PRO1082 polypeptide is a full-length or mature native sequence PRO1082 polypeptide comprising amino acids 1 through 201 of Figure 202 (SEQ ID NO:477), the native sequence PRO1083 polypeptide is a full-length or mature native sequence PRO1083 polypeptide comprising amino acids 1 or 26 through 693 of Figure 204 (SEQ ID NO:483), the native sequence VEGF-E polypeptide is a mature or full-length 25 native sequence VEGF-E polypeptide comprising amino acids 1 through 345 as depicted in Figure 207 (SEQ ID NO:488), the native sequence PRO285 is a mature or full-length native sequence PRO285 polypeptide comprising amino acids 1 to 1049 of Figure 209 (SEQ ID NO:496), the native sequence PRO286 is a mature or full-length native sequence PRO286 polypeptide comprising amino acids 1 to 1041 of Figure 211 (SEQ ID NO:298), the native sequence PRO298 is a mature or full-length native sequence PRO298 comprising amino acids 1 to 364 of Figure 219 30 (SEQ ID NO:515), the native sequence PRO337 is a mature or full-length native sequence human neurotrimin comprising amino acids 1 to 344 of Figure 222 (SEQ ID NO:523), with or without the N-terminal signal sequence (residues 1 to about 28), and with or without the initiating methionine at position 1 and the native sequence PRO403 is a mature or full-length native sequence comprising amino acids 1 to 736 of Figure 225 (SEQ ID NO:526), with or without the initiating methionine at position 1.

35 The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic

domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either or the transmembrane domain as initially identified.

- "PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 5 80% amino acid sequence identity with the full-length native sequence PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80% amino acid sequence identity, more preferably at least about 85% amino acid sequence identity, and even more preferably at least about 90% amino acid sequence identity, even more 10 preferably at least about 91% amino acid sequence identity, even more preferably at least about 92% amino acid sequence identity, even more preferably at least about 93% amino acid sequence identity, even more preferably at least about 94% amino acid sequence identity, even more preferably at least about 95% amino acid sequence identity, yet more preferably at least about 96% amino acid sequence identity, yet more preferably at least about 97% amino acid sequence identity, yet more preferably at least about 98% amino acid sequence identity and most preferably at 15 least about 99% amino acid sequence identity with the amino acid sequence of the full-length native amino acid sequence as disclosed herein.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, 20 to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. The preferred software alignment program is BLAST. Those skilled in the art can determine appropriate parameters for measuring alignment, including any 25 algorithms needed to achieve maximal alignment over the full length of the sequences being compared. The % identity values used herein have been generated using the WU-BLAST-2 computer program (Altschul et al., *Methods in Enzymology* 266:460-480 (1996); <http://blast.wustl.edu/blast/README.html>). Most of the WU-BLAST-2 search parameters were set to the default values. The adjustable parameters were set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. The HSP S and HSP 30 S2 parameters, which are dynamic values used by BLAST-2, are established by the program itself depending upon the composition of the sequence of interest and composition of the database against which the sequence is being searched. However, the values may be adjusted to increase sensitivity. A % sequence identity value is determined by the fraction of matching identical residues divided by the total number of residues in the aligned region.

"Percent (%) nucleic acid sequence identity" with respect to PRO-encoding nucleic acid sequences identified 35 herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the PRO nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art

can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. The identity values used herein were generated by the BLASTN module of WU-BLAST-2 set to the default parameters, with overlap span and overlap fraction set to 1 and 0.125, respectively.

5 The term "positives", in the context of sequence comparison performed as described above, includes residues in the sequences compared that are not identical but have similar properties (e.g. as a result of conservative substitutions). The % value of positives is determined by the fraction of residues scoring a positive value in the BLOSUM 62 matrix divided by the total number of residues in the aligned region, as defined above.

10 The term "epitope tagged" where used herein refers to a chimeric polypeptide comprising a PRO polypeptide, or domain sequence thereof, fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody may be made, or which can be identified by some other agent, yet is short enough such that it does not interfere with the activity of the PRO polypeptide of interest. The tag polypeptide preferably is also fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 to about 50 amino acid residues (preferably, between about 10 to about 20 residues).

15 "Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the PRO polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

20 An "isolated" PRO polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the PRO polypeptide nucleic acid. An isolated PRO polypeptide nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated PRO polypeptide nucleic acid molecules therefore are distinguished from the specific PRO polypeptide nucleic acid molecule as it exists in natural cells. However, an isolated PRO polypeptide nucleic acid molecule includes PRO polypeptide nucleic acid molecules contained in cells that ordinarily express the PRO polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

25 The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

30 Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is

operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

5 The term "antibody" is used in the broadest sense and specifically covers single anti-PRO polypeptide monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies) and anti-PRO polypeptide antibody compositions with polyepitopic specificity. The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

10 "Active" or "activity" for the purposes herein refers to form(s) of PRO polypeptide which retain the biologic and/or immunologic activities of the specific native or naturally-occurring PRO polypeptide.

"Treatment" or "treating" refers to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in which the disorder is to be prevented.

15 "Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as sheep, dogs, horses, cats, cows, and the like. Preferably, the mammal herein is a human.

20 "Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, 25 or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

30 The term "agonist" is used to refer to peptide and non-peptide analogs of the native PRO polypeptides (where native PRO polypeptide refers to pro-PRO polypeptide, pre-PRO polypeptide, prepro-PRO polypeptide, or mature PRO polypeptide) of the present invention and to antibodies specifically binding such native PRO polypeptides, provided that they retain at least one biological activity of a native PRO polypeptide. Preferably, the agonists of the present invention retain the qualitative binding recognition properties and receptor activation properties of the native PRO polypeptide.

35 The term "antagonist" is used to refer to a molecule inhibiting a biological activity of a native PRO polypeptide of the present invention wherein native PRO polypeptide refers to pro-PRO polypeptide, pre-PRO polypeptide, prepro-PRO polypeptide, or mature PRO polypeptide. Preferably, the antagonists herein inhibit the binding of a native PRO polypeptide of the present invention to a binding partner. A PRO polypeptide "antagonist" is a molecule which prevents, or interferes with, a PRO antagonist effector function (*e.g.* a molecule which prevents or interferes with binding and/or activation of a PRO polypeptide receptor by PRO polypeptide). Such molecules can be screened for their ability to competitively inhibit PRO polypeptide receptor activation by monitoring binding

of native PRO polypeptide in the presence and absence of the test antagonist molecule, for example. An antagonist of the invention also encompasses an antisense polynucleotide against the PRO polypeptide gene, which antisense polynucleotide blocks transcription or translation of the PRO polypeptide gene, thereby inhibiting its expression and biological activity.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel *et al.*, Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" means (1) employing low ionic strength and high temperature for washing, for example, 0.015 sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C, or (2) employing during hybridization a denaturing agent, such as formamide, for example, 50% (vol/vol) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 nM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C. Another example is use of 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6/8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC and 0.1% SDS. Yet another example is hybridization using a buffer of 10% dextran sulfate, 2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" are described in Sambrook *et al.*, *supra*, and include the use of a washing solution and hybridization conditions (e.g., temperature, ionic strength, and %SDS) less stringent than described above. An example of moderately stringent conditions is a condition such as overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/mL denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc., as necessary to accommodate factors such as probe length and the like.

"Southern analysis" or "Southern blotting" is a method by which the presence of DNA sequences in a restriction endonuclease digest of DNA or a DNA-containing composition is confirmed by hybridization to a known, labeled oligonucleotide or DNA fragment. Southern analysis typically involves electrophoretic separation of DNA digests on agarose gels, denaturation of the DNA after electrophoretic separation, and transfer of the DNA to nitrocellulose, nylon, or another suitable membrane support for analysis with a radiolabeled, biotinylated, or enzyme-labeled probe as described in sections 9.37-9.52 of Sambrook *et al.*, Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989).

"Northern analysis" or "Northern blotting" is a method used to identify RNA sequences that hybridize to a known probe such as an oligonucleotide, DNA fragment, cDNA or fragment thereof, or RNA fragment. The probe is labeled with a radioisotope such as ³²P, or by biotinylation, or with an enzyme. The RNA to be analyzed is usually

electrophoretically separated on an agarose or polyacrylamide gel, transferred to nitrocellulose, nylon, or other suitable membrane, and hybridized with the probe, using standard techniques well known in the art such as those described in sections 7.39-7.52 of Sambrook *et al.*, *supra*.

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains.

- 5 Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, 10 or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

- 15 Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

As used herein, "vascular endothelial cell growth factor-E," or "VEGF-E," refers to a mammalian growth factor as described herein, including the human amino acid sequence of Figure 207, a sequence which has homology to VEGF and bone morphogenetic protein 1 and which includes complete conservation of all VEGF cysteine residues, which have been shown to be required for biological activity of VEGF. VEGF-E expression includes expression in 20 human fetal bone, thymus, and the gastrointestinal tract. The biological activity of native VEGF-E is shared by any analogue or variant thereof that is capable of promoting selective growth and/or survival of umbilical vein endothelial cells, induces proliferation of pluripotent fibroblast cells, induces immediate early gene c-fos in human endothelial cell lines and causes myocyte hypertrophy in cardiac cells, or which possesses an immune epitope that is immunologically cross-reactive with an antibody raised against at least one epitope of the corresponding native VEGF-E. 25 The human VEGF-E herein is active on rat and mouse cells indicating conservation across species. Moreover, the VEGF-E herein is expressed at the growth plate region and has been shown to embrace fetal myocytes.

As used herein, "vascular endothelial cell growth factor," or "VEGF," refers to a mammalian growth factor as defined in U.S. Patent 5,332,671. The biological activity of native VEGF is shared by any analogue or variant thereof that is capable of promoting selective growth of vascular endothelial cells but not of bovine corneal endothelial 30 cells, lens epithelial cells, adrenal cortex cells, BHK-21 fibroblasts, or keratinocytes, or that possesses an immune epitope that is immunologically cross-reactive with an antibody raised against at least one epitope of the corresponding native VEGF.

The terms "VEGF-E polypeptide" and "VEGF-E" when used herein encompass native sequence VEGF-E polypeptide and VEGF-E polypeptide variants (which are further defined herein). The VEGF-E polypeptides may 35 be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods.

Inhibitors of VEGF-E include those which reduce or inhibit the activity or expression of VEGF-E and includes antisense molecules.

The abbreviation "KDR" refers to the kinase domain region of the VEGF molecule. VEGF-E has no homology with VEGF in this domain.

The abbreviation "FLT-1" refers to the FMS-like tyrosine kinase binding domain which is known to bind to the corresponding FLT-1 receptor. VEGF-E has no homology with VEGF in this domain.

"Toll receptor2", "TLR2" and "huTLR2" are used interchangeably, and refer to a human Toll receptor 5 designated as "HuTLR2" by Rock *et al.*, Proc. Natl. Acad. Sci. USA 95, 588-593 (1998).

The term "expression vector" is used to define a vector, in which a nucleic acid encoding a PRO polypeptide herein is operably linked to control sequences capable of affecting its expression is a suitable host cells. Vectors ordinarily carry a replication site (although this is not necessary where chromosomal integration will occur). Expression vectors also include marker sequences which are capable of providing phenotypic selection in transformed 10 cells. For example, *E. coli* is typically transformed using pBR322, a plasmid derived from an *E. coli* species (Bolivar, *et al.*, Gene 2: 95 [1977]). pBR322 contains genes for ampicillin and tetracycline resistance and thus provides easy means for identifying transformed cells, whether for purposes of cloning or expression. Expression vectors also optimally will contain sequences which are useful for the control of transcription and translation, e.g., promoters and Shine-Dalgarno sequences (for prokaryotes) or promoters and enhancers (for mammalian cells). The 15 promoters may be, but need not be, inducible; even powerful constitutive promoters such as the CMV promoter for mammalian hosts have been found to produce the LHR without host cell toxicity. While it is conceivable that expression vectors need not contain any expression control, replicative sequences or selection genes, their absence may hamper the identification of hybrid transformants and the achievement of high level hybrid immunoglobulin expression.

20 The term "lipopolysaccharide" or "LPS" is used herein as a synonym of "endotoxin." Lipopolysaccharides (LPS) are characteristic components of the outer membrane of Gram-negative bacteria, e.g., *Escherichia coli*. They consist of a polysaccharide part and a fat called lipid A. The polysaccharide, which varies from one bacterial species to another, is made up of the O-specific chain (built from repeating units of three to eight sugars) and the two-part core. Lipid A virtually always includes two glucosamine sugars modified by phosphate and a variable number of fatty 25 acids. For further information see, for example, Rietschel and Brade, Scientific American August 1992, 54-61.

30 The term "septic shock" is used herein in the broadest sense, including all definitions disclosed in Bone, Ann. Intern. Med. 114, 332-333 (1991). Specifically, septic shock starts with a systemic response to infection, a syndrome called sepsis. When this syndrome results in hypotension and organ dysfunction, it is called septic shock. Septic shock may be initiated by gram-positive organisms and fungi, as well as endotoxin-containing Gram-negative 35 organisms. Accordingly, the present definition is not limited to "endotoxin shock."

The phrases "gene amplification" and "gene duplication" are used interchangeably and refer to a process by which multiple copies of a gene or gene fragment are formed in a particular cell or cell line. The duplicated region (a stretch of amplified DNA) is often referred to as "amplicon". Usually, the amount of the messenger RNA (mRNA) produced, i.e., the level of gene expression, also increases in the proportion of the number of copies made 35 of the particular gene expressed.

"Tumor", as used herein, refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues. The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples

of such cancers include breast cancer, prostate cancer, colon cancer, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells 5 and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g. I131, I125, Y90 and Re186), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of 10 chemotherapeutic agents include adriamycin, doxorubicin, epirubicin, 5-fluorouracil, cytosine arabinoside ("Ara-C"), cyclophosphamide, thiotepa, busulfan, cytoxin, taxoids, e.g. paclitaxel (Taxol, Bristol-Myers Squibb Oncology, Princeton, NJ), and doxetaxel (Taxotere®, Rhone-Poulenc Rorer, Antony, France), toxotere, methotrexate, cisplatin, melphalan, vinblastine, bleomycin, etoposide, ifosfamide, mitomycin C, mitoxantrone, vincristine, vinorelbine, carboplatin, teniposide, daunomycin, carminomycin, aminopterin, dactinomycin, mitomycins, esperamicins (see U.S. Pat. No. 4,675,187), melphalan and other related nitrogen mustards. Also included in this definition are hormonal 15 agents that act to regulate or inhibit hormone action on tumors such as tamoxifen and onapristone.

A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially cancer cell overexpressing any of the genes identified herein, either *in vitro* or *in vivo*. Thus, the growth inhibitory agent is one which significantly reduces the percentage of cells overexpressing such genes in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than 20 S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxol, and topo II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in *The Molecular Basis of Cancer*, Mendelsohn and Israel, eds., Chapter 1, entitled 25 "Cell cycle regulation, oncogens, and antineoplastic drugs" by Murakami et al. (WB Saunders: Philadelphia, 1995), especially p.13.

"Doxorubicin" is an anthracycline antibiotic.

The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide 30 hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; and the like. As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

"Immunological cross-reactivity" as used herein means that the candidate polypeptide is capable of 35 competitively inhibiting the qualitative biological activity of a PRO213-1, PRO1330, or PRO1449 polypeptide having this activity with polyclonal antisera raised against the known active PRO213-1, PRO1330, or PRO1449 polypeptide. Such antisera may be prepared in conventional fashion by injecting goats or rabbits, for example, subcutaneously with the known active analogue in complete Freund's adjuvant, followed by booster intraperitoneal or subcutaneous injection in incomplete Freunds. The immunological cross-reactivity preferably is "specific", which means that the

binding affinity of the immunological cross-reactive molecule (e.g., antibody) identified, to the corresponding PRO213-1, PRO1330, or PRO1449 polypeptide is significantly higher (preferably at least about 2-times, more preferably at least about 4-times, even more preferably at least about 6-times, most preferably at least about 8-times higher) than the binding affinity of that molecule to any other known native polypeptide.

"Native antibodies" and "native immunoglobulins" are usually heterotetrameric glycoproteins of about 5 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant 10 domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form 15 an interface between the light- and heavy-chain variable domains.

The term "variable" refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular 20 antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called complementarity-determining regions (CDRs) or hypervariable regions both in the light-chain and the heavy-chain variable domains. The more highly conserved portions of variable domains are called the framework (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a β -sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the β -sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of 25 antibodies (see Kabat et al., NIH Publ. No.91-3242, Vol. I, pages 647-669 (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent cellular toxicity.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable 30 region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear antibodies (Zapata et al. , Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, 35 each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')2 fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. 40 It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the VH-VL dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')2 antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

5 The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, 10 and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

15 "Single-chain Fv" or "sFv" antibody fragments comprise the VH and VL domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv see Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

20 The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) in the same polypeptide chain (VH - VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

25 An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one 30 component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

35 The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labelled" antibody. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

By "solid phase" is meant a non-aqueous matrix to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a

purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as the anti-ErbB2 antibodies disclosed herein and, optionally, a chemotherapeutic agent) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the 5 lipid arrangement of biological membranes.

II. Compositions and Methods of the Invention

1. Full-length PRO213 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO213. In particular, Applicants have identified and isolated cDNA 10 encoding a PRO213 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that a portion of the PRO213 polypeptide has significant homology with the human growth arrest-specific 6 (gas6) protein. Accordingly, it is presently believed that PRO213 polypeptide disclosed in the present application may have the same or similar activity as does the gas6 protein.

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2. Full-length PRO274 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO274. In particular, Applicants have identified and isolated cDNA 20 encoding a PRO274 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO274 polypeptide have significant homology with the 7 transmembrane segment receptor proteins and Fn54 protein. Accordingly, it is presently believed that PRO274 polypeptide disclosed in the present application is a newly identified member of the 7 transmembrane segment receptor protein and/or Fn54 protein family.

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3. Full-length PRO300 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO300. In particular, Applicants have identified and isolated cDNA 30 encoding a PRO300 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO300 polypeptide have significant homology with the human Diff 33 protein. Accordingly, it is presently believed that PRO300 polypeptide disclosed in the present application is a newly identified member of the Diff 33 family.

4. Full-length PRO284 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO284. In particular, Applicants have identified and isolated cDNA 35 encoding a PRO284 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the UNQ247 (DNA23318-1211) nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, no sequence identities to any known proteins were revealed.

5. Full-length PRO296 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO296. In particular, Applicants have identified and isolated cDNA encoding a PRO296 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO296 polypeptide has significant similarity to 5 the sarcoma-amplified SAS protein. Accordingly, it is presently believed that PRO296 polypeptide disclosed in the present application is a newly identified SAS protein homolog.

6. Full-length PRO329 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides 10 referred to in the present application as PRO329. In particular, Applicants have identified and isolated cDNA encoding a PRO329 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO329 polypeptide has significant similarity to a high affinity immunoglobulin F_c receptor. Accordingly, it is presently believed that PRO329 polypeptide disclosed in the present application is a newly identified F_c receptor homolog.

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7. Full-length PRO362 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO362. In particular, Applicants have identified and isolated cDNA encoding a PRO362 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA 20 sequence alignment computer programs, Applicants found that the PRO362 polypeptide has significant similarity to the A33 antigen protein as well as the HCAR protein and the NrCAM related cell adhesion molecule. Accordingly, it is presently believed that PRO362 polypeptide disclosed in the present application is a newly A33 antigen and HCAR protein homolog.

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8. Full-length PRO363 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO363. In particular, Applicants have identified and isolated cDNA encoding a PRO363 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO363 polypeptide has significant similarity to 30 the cell surface protein HCAR. Accordingly, it is presently believed that PRO363 polypeptide disclosed in the present application is a newly HCAR homolog.

9. Full-length PRO868 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides 35 referred to in the present application as PRO868. In particular, Applicants have identified and isolated cDNA encoding a PRO868 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO868 polypeptide has significant similarity to the tumor necrosis factor receptor. Accordingly, it is presently believed that PRO868 polypeptide disclosed in the present application is a newly identified member of the tumor necrosis factor receptor family of proteins.

10. **Full-length PRO382 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO382. In particular, Applicants have identified and isolated cDNA encoding a PRO382 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the native PRO382 polypeptide shares significant homology with various serine protease proteins. Applicants have also found that the DNA encoding the PRO382 polypeptide shares significant homology with nucleic acid encoding various serine protease proteins. Accordingly, it is presently believed that PRO382 polypeptide disclosed in the present application is a newly identified serine protease homolog.

10 11. **Full-length PRO545 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO545. In particular, Applicants have identified and isolated cDNA encoding a PRO545 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO545 polypeptide have significant homology with the sequences identified designated as; human metalloproteinase ("P_W01825"), mouse meltrin alpha ("S60257"), metalloprotease-disintegrin meltrin-alpha ("GEN13695"), ADAM 13 - *Xenopus laevis* ("XLU66003_1"), mouse meltrin beta ("S60258"), rabbit metalloprotease-disintegrin meltrin-beta, ("GEN13696"), human meltrin S ("AF023477_1"), human meltrin precursor ("AF023476_1"), human ADAM 21 ("AF029900_1"), and human ADAM 20 ("AF029899_1"), thereby indicating that PRO545 may be a novel meltrin protein. Accordingly, it is presently believed that the PRO545 polypeptide disclosed in the present application is a newly identified member of the meltrin family and possesses the cellular adhesiveness typical of the meltrin proteins which comprise both metalloprotease and disintegrin domains.

12. **Full-length PRO617 Polypeptides**

25 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO617. In particular, Applicants have identified and isolated cDNA encoding a PRO617 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO617 polypeptide shares significant homology with the CD24 protein. Applicants have also found that the DNA encoding the PRO617 polypeptide has significant homology with DNA encoding the CD24 protein. Accordingly, it is presently believed that PRO617 polypeptide disclosed in the present application is a newly identified CD24 homolog.

13. **Full-length PRO700 Polypeptides**

35 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO700. In particular, Applicants have identified and isolated cDNA encoding a PRO700 polypeptide, as disclosed in further detail in the Examples below. Analysis of the amino acid sequence of the full-length PRO700 polypeptide using BLAST and FastA sequence alignment computer programs, suggests that various portions of the PRO700 polypeptide possess significant sequence similarity to various protein disulfide isomerases. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced

significant sequence similarity between the PRO700 amino acid sequence and the following Dayhoff sequences; polypeptide with protein disulfide isomerase activity, designated as ("P_P80664"), human PDI, designated as ("P_R51696"), human PDI, designated as (P_R25297"), probable protein disulfide isomerase er-60 precursor, designated as ("ER60_SCHMA"), protein disulfide isomerase precursor - *Drosophila melanogaster*, designated as ("PDI_DROME"), protein disulfide-isomerase precursor - *Nicotiana tabacum*, designated as ("NTPDIGENE_1"), 5 protein disulfide isomerase - *Onchocerca volvulus*, designated as ("OVU12440_1"), human probable protein disulfide isomerase p5 precursor , designated as ("ERP5_HUMAN"), human protein disulfide isomerase-related protein 5, ("HSU79278_1 "), and protein disulfide isomerase precursor / prolyl 4- hydroxy, ("PDI_HUMAN"), thereby indicating that PRO700 may be a novel protein disulfide isomerase. Accordingly, it is presently believed that PRO700 polypeptide disclosed in the present application is a newly identified member of the protein disulfide 10 isomerase family and possesses the ability to catalyze the formation of disulfide bonds typical of the protein disulfide isomerase family.

14. Full-length PRO702 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides 15 referred to in the present application as PRO702. In particular, Applicants have identified and isolated cDNA encoding a PRO702 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO702 polypeptide has significant similarity to the conglutinin protein. Accordingly, it is presently believed that PRO702 polypeptide disclosed in the present application is a newly identified conglutinin homolog.

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15. Full-length PRO703 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO703. In particular, Applicants have identified and isolated cDNA encoding a PRO703 polypeptide, as disclosed in further detail in the Examples below. Analysis of the amino acid 25 sequence of the full-length PRO703 polypeptide using BLAST and FastA sequence alignment computer programs, suggests that various portions of the PRO703 polypeptide possess significant sequence similarity to the VLCAS protein, thereby indicating that PRO703 may be a novel VLCAS protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant sequence similarity between the PRO703 amino acid sequence and the following Dayhoff sequences, human mRNA for very-long-chain acyl-CoA, ("D88308"), rat 30 mRNA for very-long-chain acyl-CoA synthetase, ("D85100"), *Mus musculus* fatty acid transport protein, ("MMU15976"), human very-long-chain acyl-CoA synthetase, ("D88308_1"), *Mus musculus* very-long-chain acyl-CoA synthetase, ("AF033031_1"), very-long-chain acyl-CoA synthetase - *Rattus*, ("D85100_1"), rat long-chain fatty acid transport protein, ("FATP_RAT"), mouse long-chain fatty acid transport protein, ("FATP_MOUSE"), probable long-chain fatty acid transport protein, ("FAT1_YEAST"), and fatty acid transporter protein, 35 ("CHY15839_2") , thereby indicating that PRO703 may be a novel VLCAS. Accordingly, it is presently believed that PRO703 polypeptide disclosed in the present application is a newly identified member of the VLCAS family and possesses the ability to facilitate the cellular transport of long and very long chain fatty acids typical of the VLCAS family.

16. Full-length PRO705 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO705. In particular, Applicants have identified and isolated cDNA encoding a PRO705 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO705 polypeptide has significant similarity to 5 the K-glycan protein. Accordingly, it is presently believed that PRO705 polypeptide disclosed in the present application is a newly identified member of the glycan family of proteoglycan proteins.

17. Full-length PRO708 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides 10 referred to in the present application as PRO708. In particular, Applicants have identified and isolated cDNA encoding a PRO708 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO708 polypeptide has significant homology with the aryl sulfatase proteins. Applicants have also found that the DNA encoding the PRO708 polypeptide has significant homology with DNA encoding the aryl sulfatase proteins. Accordingly, it is presently believed that 15 PRO708 polypeptide disclosed in the present application is a newly identified aryl sulfatase homolog.

18. Full-length PRO320 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO320. In particular, Applicants have identified and isolated cDNA 20 encoding a PRO320 polypeptide, as disclosed in further detail in the Examples below. Analysis of the amino acid sequence of the full-length PRO320 polypeptide using BLAST and FastA sequence alignment computer programs, suggests that various portions of the PRO320 polypeptide have significant homology to the fibulin protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO320 amino acid sequence and the following Dayhoff sequences, human fibulin-2 precursor, 25 designated "FBL2_HUMAN", human fibulin-1 isoform a precursor, designated "FBLA_HUMAN", ZK783.1 - Caenorhabditis elegans, designated "CELZK783_1", human-notch2, designated "HSU77493_1", Nel protein precursor - ratus norvegicus, designated "NEL_RAT", Mus musculus cell surface protein, designated "D32210_1", mouse (fragment) Notch B protein, designated "A49175", C50H2.3a - Caenorhabditis elegans, designated "CEC50H2_3", MEC-9L - Caenorhabditis elegans, designated "CEU33933_1", and Mus musculus notch 4, 30 designated "10 MMMHC29N7_2", thereby indicating that PRO320 may be a novel fibulin or fibulin-like protein. Accordingly, it is presently believed that PRO320 polypeptide disclosed in the present application is a newly identified member of the fibulin family and possesses biological activity typical of the fibulin family.

19. Full-length PRO324 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides 35 referred to in the present application as PRO324. In particular, Applicants have identified and isolated cDNA encoding a PRO324 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO324 polypeptide has significant similarity to oxidoreductases. Accordingly, it is presently believed that PRO324 polypeptide disclosed in the present application

is a newly identified oxidoreductase homolog.

20. Full-length PRO351 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO351. In particular, Applicants have identified and isolated cDNA encoding a PRO351 polypeptide, as disclosed in further detail in the Examples below. Analysis of the amino acid sequence of the full-length PRO351 polypeptide using BLAST and FastA sequence alignment computer programs, suggests that various portions of the PRO351 polypeptide possess significant sequence similarity to the prostasin protein, thereby indicating that PRO351 may be a novel prostasin protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant sequence similarity between the PRO351 amino acid sequence and the following Dayhoff sequences, "AC003965_1", "CELC07G1_7", "GEN12917", "HEPS_HUMAN", "GEN14584", "MCT6_MOUSE", "HSU75329_1", "PLMN_ERIEU", "TRYB_HUMAN", and "P_W22987". Accordingly, it is presently believed that PRO351 polypeptide disclosed in the present application is a newly identified member of the prostasin family and possesses properties and activities typical of the prostasin family.

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21. Full-length PRO352 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO352. In particular, Applicants have identified and isolated cDNA encoding a PRO352 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO352 polypeptide has significant similarity to the butyrophilin protein. Accordingly, it is presently believed that PRO352 polypeptide disclosed in the present application is a newly identified butyrophilin homolog.

22. Full-length PRO381 Polypeptides

25 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO381. In particular, Applicants have identified and isolated cDNA encoding a PRO381 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO381 polypeptide has significant similarity to immunophilin proteins. Accordingly, it is presently believed that PRO381 polypeptide disclosed in the present application is a newly identified FKBP immunophilin homolog.

23. Full-length PRO386 Polypeptides

35 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO386. In particular, Applicants have identified and isolated cDNA encoding a PRO386 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO386 polypeptide has significant similarity to the beta-2 subunit of a sodium channel protein. Accordingly, it is presently believed that PRO386 polypeptide disclosed in the present application is homolog of a beta-2 subunit of a sodium channel expressed in mammalian cells.

24. Full-length PRO540 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO540. In particular, Applicants have identified and isolated cDNA encoding a PRO540 polypeptide, as disclosed in further detail in the Examples below. Analysis of the amino acid sequence of the full-length PRO540 polypeptide using BLAST and FastA sequence alignment computer programs, 5 suggests that various portions of the PRO540 polypeptide possess significant sequence similarity to the LCAT protein, thereby indicating that PRO540 may be a novel LCAT protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant sequence similarity between the PRO540 amino acid sequence and the following Dayhoff sequences, phosphatidylcholine-sterol acyltransferase, designated "LCAT_HUMAN", hypothetical 75.4 kd protein, designated "YN84_YEAST", *Bacillus licheniformis* esterase, 10 designated "BLU35855_1", macrotetrolide resistance protein - *Streptomyces*, designated "JH0655", T-cell receptor delta chain precursor, designated "C30583", Rhesus kringle 2, designated "P_W07551", RAGE-1 ORF5, designated "HSU46191_3", human Ig kappa chain VKIII-JK3, designated "HSU07466_1", and *Alstroemeria inodora* reverse transcriptase, designated "ALI223606_1". Accordingly, it is presently believed that PRO540 polypeptide disclosed 15 in the present application is a newly identified member of the LCAT protein family and possesses lipid transport capability typical of the LCAT family.

25. Full-length PRO615 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO615. In particular, Applicants have identified and isolated cDNA 20 encoding a PRO615 polypeptide, as disclosed in further detail in the Examples below. Analysis of the amino acid sequence of the full-length PRO615 polypeptide using BLAST and FastA sequence alignment computer programs, suggests that various portions of the PRO615 polypeptide possess significant sequence similarity to the human synaptogyrin protein, thereby indicating that PRO615 may be a novel synaptogyrin protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant sequence similarity between the 25 PRO615 amino acid sequence and the following Dayhoff sequences, "AF039085_1", "RNU39549_1", "CELT08A9_8", "FSU62028_1", "S73645", "Y348_MYCPN", "AC000103_5", "", "RT12_LEITA", and "EBVLMP218_1". Accordingly, it is presently believed that PRO615 polypeptide disclosed in the present application 30 is a newly identified member of the synaptogyrin family and possesses activity and properties typical of the synaptogyrin family.

26. Full-length PRO618 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO618. In particular, Applicants have identified and isolated cDNA encoding a PRO618 polypeptide, as disclosed in further detail in the Examples below. Analysis of the amino acid 35 sequence of the full-length PRO618 polypeptide using BLAST and FastA sequence alignment computer programs, suggests that various portions of the PRO618 polypeptide possess significant sequence similarity to the enteropeptidase protein, thereby indicating that PRO618 may be a novel enteropeptidase. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant sequence similarity between the PRO618 amino acid sequence and the following Dayhoff sequences, "P_W22987", "KAL_HUMAN",

"AC003965_1", "GEN12917", "ENTK_HUMAN", "FA11_HUMAN", "HSU75329_1", "P_W22986", and "PLMN_HORSE". Accordingly, it is presently believed that PRO618 polypeptide disclosed in the present application is a newly identified member of the enteropeptidase family and possesses catalytic activity typical of the enteropeptidase family.

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27. Full-length PRO719 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO719. In particular, Applicants have identified and isolated cDNA encoding a PRO719 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO719 polypeptide has significant similarity to 10 the lipoprotein lipase H protein. Accordingly, it is presently believed that PRO719 polypeptide disclosed in the present application is a newly identified lipoprotein lipase H homolog.

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28. Full-length PRO724 Polypeptides

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The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO724. In particular, Applicants have identified and isolated cDNA encoding a PRO724 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO724 polypeptide has significant similarity to the human low density lipoprotein (LDL) receptor protein. Accordingly, it is presently believed that PRO724 polypeptide disclosed in the present application is a newly identified LDL receptor homolog.

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29. Full-length PRO772 Polypeptides

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The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO772. In particular, Applicants have identified and isolated cDNA encoding a PRO772 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO772 polypeptide has significant similarity to the human A4 protein. Accordingly, it is presently believed that PRO772 polypeptide disclosed in the present application is a newly identified A4 protein homolog.

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30. Full-length PRO852 Polypeptides

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The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO852. In particular, Applicants have identified and isolated cDNA encoding a PRO852 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO852 polypeptide has significant similarity to various protease proteins. Accordingly, it is presently believed that PRO852 polypeptide disclosed in the present application is a newly identified protease enzyme homolog.

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31. Full-length PRO853 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO853. In particular, Applicants have identified and isolated cDNA

encoding a PRO853 polypeptide, as disclosed in further detail in the Examples below. Analysis of the amino acid sequence of the full-length PRO853 polypeptide using BLAST and FastA sequence alignment computer programs, suggests that various portions of the PRO853 polypeptide possess significant sequence similarity to the reductase protein, thereby indicating that PRO853 may be a novel reductase. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant sequence similarity between the PRO853 amino acid sequence and the following Dayhoff sequences, "P_W03198", "CEC15H11_6", "MTV030_12", "P_W15759", "S42651", "ATAC00234314", "MTV022_13", "SCU43704_1", "CELE04F6_7", and "ALFA_1". Accordingly, it is presently believed that PRO853 polypeptide disclosed in the present application is a newly identified member of the reductase family and possesses the antioxidant enzymatic activity typical of the reductase family.

10 32. Full-length PRO860 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO860. In particular, Applicants have identified and isolated cDNA encoding a PRO860 polypeptide, as disclosed in further detail in the Examples below. Analysis of the amino acid sequence of the full-length PRO860 polypeptide using BLAST and FastA sequence alignment computer programs, suggests that various portions of the PRO860 polypeptide possess significant sequence similarity to the neurofascin protein, thereby indicating that PRO860 may be a novel neurofascin. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant sequence similarity between the PRO860 amino acid sequence and the following Dayhoff sequences, "AF040990_1", "AF041053_1", "CELZK377_2", "RNU81035_1", "D86983_1", "S26180", "MMBIG2A_1", "S46216", and "RNU68726_1". Accordingly, it is presently believed that PRO860 polypeptide disclosed in the present application is a newly identified member of the neurofascin family and possesses the cellular adhesion properties typical of the neurofascin family.

33. Full-length PRO846 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO846. In particular, Applicants have identified and isolated cDNA encoding a PRO846 polypeptide, as disclosed in further detail in the Examples below. Analysis of the amino acid sequence of the full-length PRO846 polypeptide using BLAST and FastA sequence alignment computer programs, suggests that various portions of the PRO846 polypeptide possess significant sequence similarity to the CMRF35 protein, thereby indicating that PRO846 may be a novel CMRF35 protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant sequence similarity between the PRO846 amino acid sequence and the following Dayhoff sequences, "CM35_HUMAN", "AF035963_1", "PIGR_RABIT", "AF043724_1", "RNU89744_1", "A52091_1", "S48841", "ELK06A9_3", and "AF049588_1". Accordingly, it is presently believed that PRO846 polypeptide disclosed in the present application is a newly identified member of the CMRF35 protein family and possesses properties typical of the CMRF35 protein family.

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34. Full-length PRO862 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO862. In particular, Applicants have identified and isolated cDNA encoding a PRO862 polypeptide, as disclosed in further detail in the Examples below. Analysis of the amino acid

sequence of the full-length PRO862 polypeptide using BLAST and FastA sequence alignment computer programs, suggests that various portions of the PRO862 polypeptide possess significant sequence similarity to the lysozyme protein, thereby indicating that PRO862 may be a novel lysozyme protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant sequence similarity between the PRO862 amino acid sequence and the following Dayhoff sequences, "P_P90343", and "LYC_HUMAN". Accordingly, it is presently believed that PRO862 polypeptide disclosed in the present application is a newly identified member of the lysozyme family and possesses catalytic activity typical of the lysozyme family.

35. Full-length PRO864 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO864. In particular, Applicants have identified and isolated cDNA encoding a PRO864 polypeptide, as disclosed in further detail in the Examples below. Analysis of the amino acid sequence of the full-length PRO864 polypeptide using BLAST and FastA sequence alignment computer programs, suggests that various portions of the PRO864 polypeptide possess significant sequence similarity to the Wnt-4 protein, thereby indicating that PRO864 may be a novel Wnt-4 protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant sequence similarity between the PRO864 amino acid sequence and the following Dayhoff sequences, "WNT4_MOUSE", "WNT3_MOUSE", "WNSA_HUMAN", "WN7B_MOUSE", "WN3A_MOUSE", "XLU66288_1", "WN13_HUMAN", "WN5B_ORYLA", "WNT2_MOUSE", and "WN7A_MOUSE". Accordingly, it is presently believed that PRO864 polypeptide disclosed in the present application is a newly identified member of the Wnt-4 protein family and possesses properties typical of the Wnt-4 protein family.

36. Full-length PRO792 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO792. In particular, Applicants have identified and isolated cDNA encoding a PRO792 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO792 polypeptide has significant similarity to the CD23 protein. Accordingly, it is presently believed that PRO792 polypeptide disclosed in the present application is a newly identified CD23 homolog.

30 37. Full-length PRO866 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO866. In particular, Applicants have identified and isolated cDNA encoding a PRO866 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO866 polypeptide has significant similarity to various mindin and spondin proteins. Accordingly, it is presently believed that PRO866 polypeptide disclosed in the present application is a newly identified mindin/spondin homolog.

38. Full-length PRO871 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO871. In particular, Applicants have identified and isolated cDNA encoding a PRO871 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO871 polypeptide has significant similarity to 5 the CyP-60 protein. Accordingly, it is presently believed that PRO871 polypeptide disclosed in the present application is a newly identified member of the cyclophilin protein family and possesses activity typical of the cyclophilin protein family.

39. Full-length PRO873 Polypeptides

10 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO873. In particular, Applicants have identified and isolated cDNA encoding a PRO873 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO873 polypeptide has significant similarity to a human liver carboxylesterase. Accordingly, it is presently believed that PRO873 polypeptide disclosed in the 15 present application is a newly identified member of the carboxylesterase family and possesses enzymatic activity typical of the carboxylesterase family.

40. Full-length PRO940 Polypeptides

20 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO940. In particular, Applicants have identified and isolated cDNA encoding a PRO940 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO940 polypeptide has significant similarity to CD33 and the OB binding protein-2. Accordingly, it is presently believed that PRO940 polypeptide disclosed in the present application is a newly CD33 and/or OB binding protein-2 homolog.

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41. Full-length PRO941 Polypeptides

30 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO941. In particular, Applicants have identified and isolated cDNA encoding a PRO941 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO941 polypeptide has significant similarity to one or more cadherin proteins. Accordingly, it is presently believed that PRO941 polypeptide disclosed in the present application is a newly identified cadherin homolog.

42. Full-length PRO944 Polypeptides

35 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO944. In particular, Applicants have identified and isolated cDNA encoding a PRO944 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO944 polypeptide has significant similarity to the CPE-R cell surface protein. Accordingly, it is presently believed that PRO944 polypeptide disclosed in the

present application is a newly identified CPE-R homolog.

43. Full-length PRO983 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO983. In particular, Applicants have identified and isolated cDNA 5 encoding a PRO983 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO983 polypeptide has significant similarity to the vesicle-associated protein, VAP-33. Accordingly, it is presently believed that PRO983 polypeptide disclosed in the present application is a newly identified member of the vesicle-associated membrane protein family and possesses activity typical of vesicle-associated membrane proteins.

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44. Full-length PRO1057 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1057. In particular, Applicants have identified and isolated cDNA 15 encoding a PRO1057 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1057 polypeptide has significant similarity to various protease proteins. Accordingly, it is presently believed that PRO1057 polypeptide disclosed in the present application is a newly identified protease homolog.

45. Full-length PRO1071 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1071. In particular, Applicants have identified and isolated cDNA 20 encoding a PRO1071 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1071 polypeptide has significant similarity to the thrombospondin protein. Accordingly, it is presently believed that PRO1071 polypeptide disclosed in the present application is a newly identified thrombospondin homolog.

46. Full-length PRO1072 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1072. In particular, Applicants have identified and isolated cDNA 30 encoding a PRO1072 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1072 polypeptide has significant similarity to various reductase proteins. Accordingly, it is presently believed that PRO1072 polypeptide disclosed in the present application is a newly identified member of the reductase protein family.

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47. Full-length PRO1075 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1075. In particular, Applicants have identified and isolated cDNA encoding a PRO1075 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1075 polypeptide has significant similarity

to protein disulfide isomerase. Accordingly, it is presently believed that PRO1075 polypeptide disclosed in the present application is a newly identified member of the protein disulfide isomerase family and possesses activity typical of that family.

48. **Full-length PRO181 Polypeptides**

5 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO181. In particular, Applicants have identified and isolated cDNA encoding a PRO181 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO181 polypeptide has significant similarity to the cornichon protein. Accordingly, it is presently believed that PRO181 polypeptide disclosed in the present
10 application is a newly identified cornichon homolog.

49. **Full-length PRO195 Polypeptides**

15 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO195. In particular, Applicants have identified and isolated cDNA encoding a PRO195 polypeptide, as disclosed in further detail in the Examples below. The PRO195-encoding clone was isolated from a human fetal placenta library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. To Applicants present knowledge, the UNQ169 (DNA26847-1395) nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, no sequence identities to any known proteins were revealed.
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50. **Full-length PRO865 Polypeptides**

25 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO865. In particular, Applicants have identified and isolated cDNA encoding a PRO865 polypeptide, as disclosed in further detail in the Examples below. The PRO865-encoding clone was isolated from a human fetal kidney library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the PRO865-encoding clone may encode a secreted factor. To Applicants present knowledge, the UNQ434 (DNA53974-1401) nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, no sequence identities to any known proteins were revealed.
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51. **Full-length PRO827 Polypeptides**

35 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO827. In particular, Applicants have identified and isolated cDNA encoding a PRO827 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO827 polypeptide has significant similarity to VLA-2 and various other integrin proteins. Accordingly, it is presently believed that PRO827 polypeptide disclosed in the present application is a novel integrin protein or splice variant thereof.

52. Full-length PRO1114 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1114. In particular, Applicants have identified and isolated cDNA encoding a PRO1114 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1114 polypeptide has significant similarity 5 to the cytokine receptor family of proteins. Accordingly, it is presently believed that PRO1114 polypeptide disclosed in the present application is a newly identified member of the cytokine receptor family of proteins and possesses activity typical of that family.

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1114 interferon receptor (UNQ557). In particular, cDNA encoding a 10 PRO1114 interferon receptor polypeptide has been identified and isolated, as disclosed in further detail in the Examples below. It is noted that proteins produced in separate expression rounds may be given different PRO numbers but the UNQ number is unique for any given DNA and the encoded protein, and will not be changed. However, for sake of simplicity, in the present specification the protein encoded by DNA57033-1403 as well as all 15 further native homologues and variants included in the foregoing definition of PRO1114 interferon receptor, will be referred to as "PRO1114 interferon receptor", regardless of their origin or mode of preparation.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1114 interferon receptor polypeptide (shown in Figure 142 and SEQ ID NO:352) has sequence identity with the other known interferon receptors. Accordingly, it is presently believed that PRO1114 interferon receptor possesses activity typical of other interferon receptors.

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53. Full-length PRO237 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO237. In particular, Applicants have identified and isolated cDNA encoding a PRO237 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO237 polypeptide has significant similarity 25 to carbonic anhydrase. Accordingly, it is presently believed that PRO237 polypeptide disclosed in the present application is a newly identified carbonic anhydrase homolog.

54. Full-length PRO541 Polypeptides

30 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO541. In particular, Applicants have identified and isolated cDNA encoding a PRO541 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO541 polypeptide has significant similarity 35 to a trypsin inhibitor protein. Accordingly, it is presently believed that PRO541 polypeptide disclosed in the present application is a newly identified member of the trypsin inhibitor protein family.

55. Full-length PRO273 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO273. In particular, Applicants have identified and isolated cDNA

encoding a PRO273 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO273 polypeptide have significant sequence identity with various chemokines. Accordingly, it is presently believed that PRO273 polypeptide disclosed in the present application is a newly identified member of the chemokine family and possesses activity typical of the chemokine family.

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56. Full-length PRO701 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO701. In particular, Applicants have identified and isolated cDNA encoding a PRO701 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO701 polypeptide have significant homology with the neuroligins 1, 2 and 3 and esterases including carboxyesterases and acetylcholinesterases. Accordingly, it is presently believed that PRO701 polypeptide disclosed in the present application is a newly identified member of the neuroligin family and is involved in mediating recognition processes between neurons and/or functions as a cell adhesin molecule as is typical of neuroligins.

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57. Full-length PRO704 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO704. In particular, Applicants have identified and isolated cDNA encoding a PRO704 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO704 polypeptide have significant homology with the VIP36 and GP36b. Accordingly, it is presently believed that PRO704 polypeptide disclosed in the present application is a newly identified member of the vesicular integral membrane protein family and possesses the ability to bind to sugars and cycle between the plasma membrane and the Golgi typical of this family.

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58. Full-length PRO706 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO706. In particular, Applicants have identified and isolated cDNA encoding a PRO706 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO706 polypeptide have sequence identity with the human prostatic acid phosphatase precursor and the human lysosomal acid phosphatase precursor. Accordingly, it is presently believed that PRO706 polypeptide disclosed in the present application is a newly identified member of the human prostatic acid phosphatase precursor family and possesses phosphatase typical of the acid phosphatase family.

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59. Full-length PRO707 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO707. In particular, Applicants have identified and isolated cDNA encoding a PRO707 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA

sequence alignment computer programs, Applicants found that various portions of the PRO707 polypeptide have significant homology with cadherins, particularly cadherin FIB3 found in fibroblasts. Accordingly, it is presently believed that PRO707 polypeptide disclosed in the present application is a newly identified member of the cadherin family and possesses cell interaction signaling typical of the cadherin family.

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60. Full-length PRO322 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO322. In particular, Applicants have identified and isolated cDNA encoding a PRO322 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO322 polypeptide have 10 significant homology with human neuropsin, serine protease, neurosin and trypsinogen. Accordingly, it is presently believed that PRO322 polypeptide disclosed in the present application is a newly identified member of the serine protease family and possesses protease activity typical of this family. It is also believed that PRO322 is involved in hippocampal plasticity and is associated with extracellular matrix modifications and cell migrations.

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61. Full-length PRO526 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO526. In particular, Applicants have identified and isolated cDNA encoding a PRO526 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO526 polypeptide have 20 significant homology with the acid labile subunit of the insulin-like growth factor complex (ALS), as well carboxypeptidase, SLIT, and platelet glycoprotein V. Accordingly, it is presently believed that PRO526 polypeptide disclosed in the present application is a newly identified member of the leucine-repeat rich superfamily, and possesses protein-protein interaction capabilities typical of this family.

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62. Full-length PRO531 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO531. In particular, Applicants have identified and isolated cDNA encoding a PRO531 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO531 polypeptide have 30 significant sequence identity and similarity with members of the cadherin superfamily, particularly, protocadherin 3. Accordingly, it is presently believed that PRO531 polypeptide disclosed in the present application is a newly identified member of the cadherin superfamily, and is a protocadherin. PRO531 is a transmembrane protein which has extracellular cadherin motifs. PRO531 is believed to be involved in cell-cell activity, in particular, cell signaling.

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63. Full-length PRO534 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO534. In particular, Applicants have identified and isolated cDNA encoding a PRO534 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO534 polypeptide have

significant identity or similarity with the putative disulfide isomerase erp38 precursor and thioredoxin c-3. Accordingly, it is presently believed that PRO534 polypeptide disclosed in the present application is a newly identified member of the disulfide isomerase family and possesses the ability to recognize and unscramble either intermediate or incorrect folding patterns typical of this family.

5 **64. Full-length PRO697 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO697. In particular, Applicants have identified and isolated cDNA encoding a PRO697 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO697 polypeptide have 10 significant identity or similarity with sFRP-2, sFRP-1 and SARP-1, -2 and -3. Accordingly, it is presently believed that PRO697 polypeptide disclosed in the present application is a newly identified member of the sFRP family and possesses activity related to the Wnt signal pathway.

15 **65. Full-length PRO717 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO717. In particular, Applicants have identified and isolated cDNA encoding a PRO717 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the UNQ385 (DNA50988-1326) nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, no significant sequence identities to any known human proteins were 20 revealed.

25 **66. Full-length PRO731 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO731. In particular, Applicants have identified and isolated cDNA 30 encoding a PRO731 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO731 polypeptide have significant homology with the protocadherins 4, 68, 43, 42, 3, and 5. Accordingly, it is presently believed that PRO731 polypeptide disclosed in the present application is a newly identified member of the protocadherin family and possesses cell-cell aggregation or signaling activity or signal transduction involvement typical of this family.

35 **67. Full-length PRO218 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO218. In particular, Applicants have identified and isolated cDNA encoding a PRO218 polypeptide, as disclosed in further detail in the Examples below. The PRO218-encoding clone was isolated from a human fetal kidney library. To Applicants present knowledge, the UNQ192 (DNA30867-1335) 35 nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, no significant sequence identities to any known proteins were revealed. Some sequence identity was found with membrane regulator proteins, indicating that PRO218 may function as a membrane regulator.

68. Full-length PRO768 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO768. In particular, Applicants have identified and isolated cDNA encoding a PRO768 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO768 polypeptide have 5 significant homology with integrins, including integrin 7 and 6. Accordingly, it is presently believed that PRO768 polypeptide disclosed in the present application is a newly identified member of the integrin family, either a homologue or a splice variant of integrin 7, and is involved with cell adhesion and communication between muscle cells and the extracellular matrix.

10 69. Full-length PRO771 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO771. In particular, Applicants have identified and isolated cDNA encoding a PRO771 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO771 polypeptide have 15 significant sequence identity and similarity with testican. Accordingly, it is presently believed that PRO771 polypeptide disclosed in the present application is a newly identified member of the testican family and possesses cell signaling, binding, or adhesion properties, typical of this family.

70. Full-length PRO733 Polypeptides

20 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO733. In particular, Applicants have identified and isolated cDNA encoding a PRO733 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO733 polypeptide have significant sequence identity with the T1/ST receptor binding protein. Accordingly, it is presently believed that 25 PRO733 polypeptide disclosed in the present application is a newly identified member of the interleukin-like family binding proteins which may be a cytokine and which may be involved in cell signaling. It is believed that PRO733 is an ApoAIV homologue.

71. Full-length PRO162 Polypeptides

30 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO162. In particular, Applicants have identified and isolated cDNA encoding a PRO162 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO162 polypeptide have significant homology with human pancreatitis-associated protein (PAP). Applicants have also found that the DNA 35 encoding the PRO162 polypeptide has significant homology with bovine lithostathine precursor and bovine pancreatic thread protein (PTP). Accordingly, it is presently believed that PRO162 polypeptide disclosed in the present application is a newly identified member of the pancreatitis-associated protein family and possesses activity typical of the pancreatitis-associated protein family.

72. Full-length PRO788 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO788. In particular, Applicants have identified and isolated cDNA encoding a PRO788 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO788 polypeptide have 5 significant homology with the anti-neoplastic urinary protein. Applicants have also found that the DNA encoding the PRO788 polypeptide has significant homology with human E48 antigen, human component B protein, and human prostate stem cell antigen. Accordingly, it is presently believed that PRO788 polypeptide disclosed in the present application is a newly identified member of the anti-neoplastic urinary protein family and possesses anti-neoplastic activity typical of the anti-neoplastic urinary protein family.

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73. Full-length PRO1008 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1008. In particular, Applicants have identified and isolated cDNA encoding a PRO1008 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO1008 polypeptide have 15 significant sequence identity and similarity with mouse dkk-1 (mdkk-1). Accordingly, it is presently believed that PRO1008 polypeptide disclosed in the present application is a newly identified member of the dkk-1 family and possesses head inducing activity typical of this family.

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74. Full-length PRO1012 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1012. In particular, Applicants have identified and isolated cDNA encoding a PRO1012 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO1012 polypeptide have 25 sequence identity with disulfide isomerase. Accordingly, it is presently believed that PRO1012 polypeptide disclosed in the present application is a newly identified member of the ER retained protein family and possesses activity related to the processing, production and/or folding of polypeptides typical of the disulfide isomerase family.

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75. Full-length PRO1014 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1014. In particular, Applicants have identified and isolated cDNA encoding a PRO1014 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO1014 polypeptide have 35 sequence identity with reductase and dehydrogenase. Accordingly, it is presently believed that PRO1014 polypeptide disclosed in the present application is a newly identified member of the reductase super family and possesses reduction capabilities typical of this family.

76. Full-length PRO1017 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1017. In particular, Applicants have identified and isolated cDNA encoding a PRO1017 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO1017 polypeptide have 5 sequence identity with HNK-1 sulfotransferase. Accordingly, it is presently believed that PRO1017 polypeptide disclosed in the present application is a newly identified member of the HNK-1 sulfotransferase family and is involved with the synthesis of HNK-1 carbohydrate epitopes typical of this family.

77. Full-length PRO474 Polypeptides

10 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO474. In particular, Applicants have identified and isolated cDNA encoding a PRO474 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO474 polypeptide have sequence identity with dehydrogenase, glucose dehydrogenase and oxidoreductase. Accordingly, it is presently 15 believed that PRO474 polypeptide disclosed in the present application is a newly identified member of the dehydrogenase family and is involved in the oxidation of glucose.

78. Full-length PRO1031 Polypeptides

20 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1031. In particular, Applicants have identified and isolated cDNA encoding a PRO1031 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO1031 polypeptide have sequence identity with IL-17 and CTLA-8. Accordingly, it is presently believed that PRO1031 polypeptide disclosed 25 in the present application is a newly identified member of the cytokine family and thus may be involved in inflammation and/or the immune system.

79. Full-length PRO938 Polypeptides

30 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO938. In particular, Applicants have identified and isolated cDNA encoding a PRO938 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO938 polypeptide has significant similarity to protein disulfide isomerase. Accordingly, it is presently believed that PRO938 polypeptide disclosed in the present application is a newly identified member of the thioredoxin family proteins and possesses activity typical of protein disulfide isomerase.

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80. Full-length PRO1082 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1082. In particular, Applicants have identified and isolated cDNA encoding a PRO1082 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA

sequence alignment computer programs. Applicants found that various portions of the PRO1082 polypeptide have sequence identity with a lectin-like oxidized LDL receptor appearing in the database as "AB010710_1". Accordingly, it is presently believed that PRO1082 polypeptide disclosed in the present application is a newly identified member of the LDL receptor family.

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81. Full-length PRO1083 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1083. In particular, Applicants have identified and isolated cDNA encoding a PRO1083 polypeptide, as disclosed in further detail in the Examples below. The PRO1083-encoding clone was isolated from a human fetal kidney library using a trapping technique which selects for nucleotide sequences 10 encoding secreted proteins. To Applicants present knowledge, the UNQ540 (DNA50921-1458) nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, some sequence identity with a 7TM receptor, latrophilin related protein 1 and a macrophage restricted cell surface glycoprotein was shown. The kinase phosphorylation site and G-coupled receptor domain shown in Figure 204 indicate that PRO1083 is a novel member of the 7TM receptor superfamily.

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82. Full-length PRO200 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as VEGF-E. In particular, Applicants have identified and isolated cDNA encoding a VEGF-E polypeptide, as disclosed in further detail in the Examples below. Using BLAST sequence 20 alignment computer programs, Applicants found that the VEGF-E polypeptide has significant homology with VEGF and bone morphogenetic protein 1. In particular, the cDNA sequence of VEGF-E exhibits 24% amino acid similarity with VEGF and has structural conservation. In addition, VEGF-E contains a N-terminal half which is not present in VEGF and that has 28% homology to bone morphogenetic protein 1.

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83. Full-length PRO285 and PRO286 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO285 and PRO286. In particular, Applicants have identified and isolated cDNAs encoding PRO285 and PRO286 polypeptides, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the coding sequences of PRO285 30 and PRO286 are highly homologous to DNA sequences HSU88540_1, HSU88878_1, HSU88879_1, HSU88880_1, and HSU88881_1 in the GenBank database.

Accordingly, it is presently believed that the PRO285 and PRO286 proteins disclosed in the present application are newly identified human homologues of the *Drosophila* protein Toll, and are likely to play an important role in adaptive immunity. More specifically, PRO285 and PRO286 may be involved in inflammation, septic shock, 35 and response to pathogens, and play possible roles in diverse medical conditions that are aggravated by immune response, such as, for example, diabetes, ALS, cancer, rheumatoid arthritis, and ulcers. The role of PRO285 and PRO286 as pathogen pattern recognition receptors, sensing the presence of conserved molecular structures present on microbes, is further supported by the data disclosed in the present application, showing that a known human Toll-like receptor, TLR2 is a direct mediator of LPS signaling.

84. Full-length PRO213-1, PRO1330 and PRO1449 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO213-1, PRO1330 and/or PRO1449. In particular, cDNA encoding a PRO213-1, PRO1330 and/or PRO1449 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below. It is noted that proteins produced in separate expression rounds may be given different PRO numbers but the UNQ number is unique for any given DNA and the encoded protein, and will not be changed. However, for sake of simplicity, in the present specification the protein encoded by DNA30943-1163-1, DNA64907-1163-1 and DNA64908-1163-1 as well as all further native homologues and variants included in the foregoing definition of PRO213-1, PRO1330 and/or PRO1449, will be referred to as "PRO213-1, PRO1330 and/or PRO1449", regardless of their origin or mode of preparation.

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85. Full-length PRO298 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO298. (It is noted that PRO298 is an arbitrary designation of a protein encoded by the nucleic acid shown in Figure 218, SEQ ID NO: 514, and having the amino acid sequence shown in Figure 219, SEQ ID NO:515. Further proteins having the same amino acid sequence but expressed in different rounds of expression, may be given different "PRO" numbers.)

In particular, Applicants have identified and isolated cDNA encoding a PRO298 polypeptide, as disclosed in further detail in the Examples below. Using BLASTX 2.0a8MP-WashU computer program, scoring parameters: T=12, S=68, S2=36, Matrix: BLOSUM62, Applicants found that the PRO298 protein specifically disclosed herein shows a limited (27-38%) sequence identity with the following sequences found in the GenBank database: S59392 (probable membrane protein YLR246w - yeast); S58154 (hypothetical protein SPAC2F7.10 - yeast); CELF33D11_9 (F33D11.9b - *Caenorhabditis elegans*); YO41_CAEEL (hypothetical 68.7 kd protein zk757.1); CEAC3_5 (AC3.4 - *Caenorhabditis elegans*); S52691 (probable transmembrane protein YDR126w - yeast); ATT12H17_14 (protein - *Arabidopsis thaliana*); S55963 (probable membrane protein YNL326c - yeast); CELC43H6_2 (C43H6.7 - *Caenorhabditis elegans*); TMO18A10_14 (A_TMO18A10.8 - *Arabinosa thaliana*).

86. Full-length PRO337 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO337. In particular, Applicants have identified and isolated cDNA encoding a PRO337 polypeptide, as disclosed in further detail in the Examples below. Using BLAST, BLAST-2 and FastA sequence alignment computer programs, Applicants found that a full-length native sequence PRO337 has 97% amino acid sequence identity with rat neurotrimin, 85% sequence identity with chicken CEPU, 73% sequence identity with chicken G55, 59% homology with human LAMP and 84% homology with human OPCAM. Accordingly, it is presently believed that PRO337 disclosed in the present application is a newly identified member of the IgLON sub family of the immunoglobulin superfamily and may possess neurite growth and differentiation potentiating properties.

87. Full-length PRO403 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO403. In particular, Applicants have identified and isolated cDNA encoding a PRO403 polypeptide, as disclosed in further detail in the Examples below. Using a BLAST, BLAST-2 and FastA sequence alignment computer programs, Applicants found that a full-length native sequence PRO403 has 5 94% identity to bovine ECE-2 and 64% identity to human ECE-1. Accordingly is presently believed that PRO403 is a new member of the ECE protein family and may posses ability to catalyze the production of active endothelin.

88. PRO Polypeptide Variants

In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO 10 polypeptide variants can be prepared. PRO polypeptide variants can be prepared by introducing appropriate nucleotide changes into the PRO polypeptide DNA, or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the PRO polypeptides, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the native full-length sequence PRO polypeptides or in various domains of the PRO 15 polypeptides described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the PRO polypeptide that results in a change in the amino acid sequence of the PRO polypeptide as compared with the native sequence PRO polypeptide. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains 20 of the PRO polypeptide. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO polypeptide with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., 25 conservative amino acid replacements. Insertions or deletions may optionally be in the range of 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity in the *in vitro* assay described in the Examples below.

In particular embodiments, conservative substitutions of interest are shown in Table 1 under the heading of 30 preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 1, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 1

<u>Original Residue</u>	<u>Exemplary Substitutions</u>	<u>Preferred Substitutions</u>
5 Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; lys; arg	gln
Asp (D)	glu	glu
Cys (C)	ser	ser
10 Gin (Q)	asn	asn
Glu (E)	asp	asp
Gly (G)	pro; ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	
15 Leu (L)	norleucine; ile; val; met; ala; phe	leu
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
20 Phe (F)	leu; val; ile; ala; tyr	leu
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Trp (W)	tyr; phe	tyr
25 Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- 35 (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

40 Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., *Nucl. Acids Res.*, 45 13:4331 (1986); Zoller et al., *Nucl. Acids Res.*, 10:6487 (1987)], cassette mutagenesis [Wells et al., *Gene*, 34:315 (1985)], restriction selection mutagenesis [Wells et al., *Philos. Trans. R. Soc. London SerA*, 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the desired PRO polypeptide variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, *The Proteins*, (W.H. Freeman & Co., N.Y.); Chothia, *J. Mol. Biol.*, 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

89. Modifications of PRO Polypeptides

Covalent modifications of PRO polypeptides are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of the PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues of the PRO polypeptide. Derivatization with bifunctional agents is useful, for instance, for crosslinking a PRO polypeptide to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO polypeptide antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate.

Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, *Proteins: Structure and Molecular Properties*, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptides included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in a native sequence PRO polypeptide, and/or adding one or more glycosylation sites that are not present in the native sequence PRO polypeptide, and/or alteration of the ratio and/or composition of the sugar residues attached to the glycosylation site(s).

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO polypeptide (for O-linked glycosylation sites). The PRO polypeptide amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the PRO polypeptide polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, *CRC Crit. Rev. Biochem.*, pp. 259-306 (1981).

Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., *Arch. Biochem. Biophys.*, 259:52 (1987) and by Edge et al., *Anal. Biochem.*, 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., *Meth. Enzymol.*, 138:350 (1987).

Another type of covalent modification of PRO polypeptides of the invention comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

The PRO polypeptides of the present invention may also be modified in a way to form a chimeric molecule comprising a PRO polypeptide fused to another, heterologous polypeptide or amino acid sequence. In one embodiment, such a chimeric molecule comprises a fusion of the PRO polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO polypeptide. The presence of such epitope-tagged forms of the PRO polypeptide can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO polypeptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO polypeptide with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule, such a fusion could be to the Fc region of an IgG molecule.

Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CAS [Field et al., *Mol. Cell. Biol.*, 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., *Molecular and Cellular Biology*, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., *Protein Engineering*, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., *BioTechnology*, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., *Science*, 255:192-194 (1992)]; an α -tubulin epitope peptide [Skinner et al., *J. Biol. Chem.*, 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., *Proc. Natl. Acad. Sci. USA*, 87:6393-6397 (1990)].

30 90. Preparation of PRO Polypeptides

The description below relates primarily to production of PRO polypeptides by culturing cells transformed or transfected with a vector containing the desired PRO polypeptide nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare the PRO polypeptide. For instance, the PRO polypeptide sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., *Solid-Phase Peptide Synthesis*, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, *J. Am. Chem. Soc.*, 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the desired PRO polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to

produce the full-length PRO polypeptide.

A. Isolation of DNA Encoding PRO Polypeptides

DNA encoding PRO polypeptides may be obtained from a cDNA library prepared from tissue believed to possess the desired PRO polypeptide mRNA and to express it at a detectable level. Accordingly, human PRO 5 polypeptide DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO polypeptide-encoding gene may also be obtained from a genomic library or by oligonucleotide synthesis.

Libraries can be screened with probes (such as antibodies to the desired PRO polypeptide or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the 10 cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding the desired PRO polypeptide is to use PCR methodology [Sambrook et al., supra; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

15 The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ³²P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are 20 provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known 25 sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined through sequence alignment using computer software programs such as BLAST, ALIGN, DNAsstar, and INHERIT which employ various algorithms to measure homology.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

30

B. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as 35 media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of transfection are known to the ordinarily skilled artisan, for example, CaPO₄ and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., *supra*, or electroporation is generally used for prokaryotes or other cells that contain substantial cell-wall barriers. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., *Gene*, 23:315 (1983) and 5 WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, *Virology*, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transformations have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., *J. Bact.*, 130:946 (1977) and Hsiao et al., *Proc. Natl. Acad. Sci. (USA)*, 76:3829 (1979). However, other methods for introducing DNA into cells, such 10 as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., *Methods in Enzymology*, 185:527-537 (1990) and Mansour et al., *Nature*, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or 15 Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and 20 *Streptomyces*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325); and K5 772 (ATCC 53,635). These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts 25 of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT karf*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP 30 ompT rbs7 ilvG karf*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or 35 expression hosts for PRO polypeptide-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, *Nature*, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., *Bio/Technology*, 9: 968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., *J. Bacteriol.*, 737 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickeramii* (ATCC 24,178),

K. waltii (ATCC 56,500), *K. drosophilicola* (ATCC 36,906; Van den Berg *et al.*, Bio/Technology, **8**: 135 (1990)), *K. thermotolerans*, and *K. marxianus*; *yarrowiae* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreeramana *et al.*, J. Basic Microbiol., **28**: 265-278 [1988]); *Candida*; *Trichoderma reesiae* (EP 244,234); *Neurospora crassa* (Case *et al.*, Proc. Natl. Acad. Sci. USA, **76**: 5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* 5 (*WO 91/00357* published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance *et al.*, Biochem. Biophys. Res. Commun., **112**: 284-289 [1983]; Tilburn *et al.*, Gene, **26**: 205-221 [1983]; Yelton *et al.*, Proc. Natl. Acad. Sci. USA, **81**: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., **4**: 475-479 [1985]). Methylotropic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and 10 *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylotrophs, 269 (1982).

Suitable host cells for the expression of glycosylated PRO polypeptides are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila S2* and *Spodoptera Sf9*, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. 15 More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham *et al.*, J. Gen. Virol., **36**:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, **77**:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., **23**:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The 20 selection of the appropriate host cell is deemed to be within the skill in the art.

C. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding a desired PRO polypeptide may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. 25 The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing 30 one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The PRO polypeptide of interest may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the PRO polypeptide DNA that is inserted into the vector. The signal 35 sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In

mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2μ plasmid origin is 5 suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not 10 available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the PRO polypeptide nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., *Proc. Natl. Acad. Sci. USA*, **77**:4216 (1980). A suitable selection gene 15 for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., *Nature*, **282**:39 (1979); Kingsman et al., *Gene*, **7**:141 (1979); Tschemper et al., *Gene*, **10**:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, *Genetics*, **85**:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the PRO polypeptide nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the β -lactamase and lactose promoter systems [Chang et al., *Nature*, **275**:615 (1978); Goeddel et al., *Nature*, **281**:544 (1979)], alkaline phosphatase, a tryptophan (*trp*) promoter system [Goeddel, *Nucleic Acids Res.*, **8**:4057 (1980); EP 36,776], and hybrid promoters such as the tac promoter [deBoer et al., *Proc. Natl. Acad. Sci. USA*, **80**:21-25 (1983)]. Promoters for use in bacterial systems also 25 will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding the desired PRO polypeptide.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., *J. Biol. Chem.*, **255**:2073 (1980)] or other glycolytic enzymes [Hess et al., *J. Adv. Enzyme Reg.*, **7**:149 (1968); Holland, *Biochemistry*, **17**:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 30 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for 35 use in yeast expression are further described in EP 73,657.

PRO polypeptide transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin

promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the desired PRO polypeptide by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the PRO polypeptide coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding PRO polypeptides.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO polypeptides in recombinant vertebrate cell culture are described in Gething et al., *Nature*, 292:620-625 (1981); Mantei et al., *Nature*, 281:40-46 (1979); EP 117,060; and EP 117,058.

D. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, *Proc. Natl. Acad. Sci. USA*, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to a PRO polypeptide DNA and encoding a specific antibody epitope.

E. Purification of Polypeptide

Forms of PRO polypeptides may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of PRO polypeptides can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify PRO polypeptides from recombinant cell proteins or polypeptides. The following

procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO polypeptide. Various methods of protein purification may be employed and such methods
5 are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO polypeptide produced.

91. Uses for PRO Polypeptides

10 Nucleotide sequences (or their complement) encoding the PRO polypeptides of the present invention have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. PRO polypeptide-encoding nucleic acid will also be useful for the preparation of PRO polypeptides by the recombinant techniques described herein.

15 The full-length native sequence PRO polypeptide-encoding nucleic acid or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length PRO polypeptide gene or to isolate still other genes (for instance, those encoding naturally-occurring variants of the PRO polypeptide or PRO polypeptides from other species) which have a desired sequence identity to the PRO polypeptide nucleic acid sequences. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be derived from the nucleotide sequence of any of the DNA molecules disclosed herein or from genomic sequences including promoters,
20 enhancer elements and introns of native sequence PRO polypeptide encoding DNA. By way of example, a screening method will comprise isolating the coding region of the PRO polypeptide gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such as ³²P or ³⁵S, or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the specific PRO
25 polypeptide gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below.

The ESTs disclosed in the present application may similarly be employed as probes, using the methods disclosed herein.

30 The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related PRO polypeptide sequences.

Nucleotide sequences encoding a PRO polypeptide can also be used to construct hybridization probes for mapping the gene which encodes that PRO polypeptide and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a
35 chromosome using known techniques, such as *in situ* hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

When the coding sequence for the PRO polypeptide encodes a protein which binds to another protein, the PRO polypeptide can be used in assays to identify its ligands. Similarly, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide

or small molecule inhibitors or agonists of the binding interaction. Screening assays can be designed to find lead compounds that mimic the biological activity of a native PRO polypeptide or a ligand for the PRO polypeptide. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

Nucleic acids which encode a PRO polypeptide or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding a PRO polypeptide of interest can be used to clone genomic DNA encoding the PRO polypeptide in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding the PRO polypeptide. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for PRO polypeptide transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding a PRO polypeptide introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding the PRO polypeptide. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

Alternatively, non-human homologues of PRO polypeptides can be used to construct a PRO polypeptide "knock out" animal which has a defective or altered gene encoding the PRO polypeptide of interest as a result of homologous recombination between the endogenous gene encoding the PRO polypeptide and altered genomic DNA encoding the PRO polypeptide introduced into an embryonic cell of the animal. For example, cDNA encoding a PRO polypeptide can be used to clone genomic DNA encoding the PRO polypeptide in accordance with established techniques. A portion of the genomic DNA encoding a PRO polypeptide can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal

contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the PRO polypeptide.

When *in vivo* administration of a PRO polypeptide is employed, normal dosage amounts may vary from about 10 ng/kg to up to 100 mg/kg of mammal body weight or more per day, preferably about 1 μ g/kg/day to 10 mg/kg/day, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature; see, for example, U.S. Pat. Nos. 4,657,760; 5,206,344; or 5,225,212. It is anticipated that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue.

Where sustained-release administration of a PRO polypeptide is desired in a formulation with release characteristics suitable for the treatment of any disease or disorder requiring administration of the PRO polypeptide, microencapsulation of the PRO polypeptide is contemplated. Microencapsulation of recombinant proteins for sustained release has been successfully performed with human growth hormone (rhGH), interferon- (rhIFN-), interleukin-2, and MN rgp120. Johnson *et al.*, Nat. Med., 2: 795-799 (1996); Yasuda, Biomed. Ther., 27: 1221-1223 (1993); Hora *et al.*, Bio/Technology, 8: 755-758 (1990); Cleland, "Design and Production of Single Immunization Vaccines Using Polylactide Polyglycolide Microsphere Systems," in Vaccine Design: The Subunit and Adjuvant Approach, Powell and Newman, eds., (Plenum Press: New York, 1995), pp. 439-462; WO 97/03692, WO 96/40072, WO 96/07399; and U.S Pat. No. 5,654,010.

The sustained-release formulations of these proteins were developed using poly-lactic-glycolic acid (PLGA) polymer due to its biocompatibility and wide range of biodegradable properties. The degradation products of PLGA, lactic and glycolic acids, can be cleared quickly within the human body. Moreover, the degradability of this polymer can be adjusted from months to years depending on its molecular weight and composition. Lewis, "Controlled release of bioactive agents from lactide/glycolide polymer," in: M. Chasin and R. Langer (Eds.), Biodegradable Polymers as Drug Delivery Systems (Marcel Dekker: New York, 1990), pp. 1-41.

For example, for a formulation that can provide a dosing of approximately 80 g/kg/day in mammals with a maximum body weight of 85 kg, the largest dosing would be approximately 6.8 mg of the PRO polypeptide per day. In order to achieve this dosing level, a sustained- release formulation which contains a maximum possible protein loading (15-20% w/w PRO polypeptide) with the lowest possible initial burst (<20%) is necessary. A continuous (zero-order) release of the PRO polypeptide from microparticles for 1-2 weeks is also desirable. In addition, the encapsulated protein to be released should maintain its integrity and stability over the desired release period.

PRO213 polypeptides and portions thereof which possess the ability to regulate the growth induction cascade and/or the blood coagulation cascade may also be employed for such purposes both *in vivo* therapy and *in vitro*. Those of ordinary skill in the art will well know how to employ PRO213 polypeptides for such uses.

PRO274 polypeptides and portions thereof which have homology to 7TM protein and Fn54 may also be useful for *in vivo* therapeutic purposes, as well as for various other applications. The identification of novel 7TM protein and Fn54-like molecules may have relevance to a number of human disorders which involve recognition of ligands and the subsequent signal transduction of information contained within those ligands in order to control cellular processes. Thus, the identification of new 7TM protein and Fn54-like molecules is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides

may also play important roles in biotechnological and medical research as well as in various industrial applications. As a result, there is particular scientific and medical interest in new molecules, such as PRO274.

PRO300 polypeptides and portions thereof which have homology to Diff 33 may also be useful for *in vivo* therapeutic purposes, as well as for various other applications. The identification of novel Diff 33-like molecules may have relevance to a number of human disorders such as the physiology of cancer. Thus, the identification of new 5 Diff 33-like molecules is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and medical research as well as various industrial applications. As a result, there is particular scientific and medical interest in new molecules, such as PRO300.

PRO296 polypeptides of the present invention which possess biological activity related to that of the 10 sarcoma-amplified SAS protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO296 polypeptides of the present invention for such purposes.

PRO329 polypeptides of the present invention which possess biological activity related to that of the immunoglobulin F_c receptor protein or subunit thereof may be employed both *in vivo* for therapeutic purposes and 15 *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO329 polypeptides of the present invention for such purposes.

PRO362 polypeptides of the present invention which possess biological activity related to that of the A33 antigen protein, HCAR protein or the NrCAM related cell adhesion molecule may be employed both *in vivo* for therapeutic purposes and *in vitro*.

20 PRO363 polypeptides of the present invention which possess biological activity related to that of the cell surface HCAR protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO363 polypeptides of the present invention for such purposes. Specifically, extracellular domains derived from the PRO363 polypeptides may be employed therapeutically *in vivo* for lessening the effects of viral infection.

25 PRO868 polypeptides of the present invention which possess biological activity related to that of the tumor necrosis factor protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO868 polypeptides of the present invention for such purposes.

30 PRO382 polypeptides of the present invention which possess biological activity related to that of the serine protease proteins may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO382 polypeptides of the present invention for such purposes.

PRO545 polypeptides and portions thereof which have homology to meltrin may also be useful for *in vivo* therapeutic purposes, as well as for various other applications. The identification of novel molecules associated with cellular adhesion may be relevant to a number of human disorders. Given that the meltrin proteins may play an important role in a number of disease processes, the identification of new meltrin proteins and meltrin-like molecules 35 is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and medical research, as well as various industrial applications. As a result, there is particular scientific and medical interest in new molecules, such as PRO545.

PRO617 polypeptides of the present invention which possess biological activity related to that of the CD24 protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO617 polypeptides of the present invention for such purposes.

PRO700 polypeptides and portions thereof which have homology to protein disulfide isomerase may also be useful for *in vivo* therapeutic purposes, as well as for various other applications. The identification of novel 5 protein disulfide isomerases and related molecules may be relevant to a number of human disorders. Given that formation of disulfide bonds and protein folding play important roles in a number of biological processes, the identification of new protein disulfide isomerases and protein disulfide isomerase-like molecules is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and medical research, as well as various industrial 10 applications. As a result, there is particular scientific and medical interest in new molecules, such as PRO700.

PRO702 polypeptides of the present invention which possess biological activity related to that of the conglutinin protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO702 polypeptides of the present invention for such purposes. PRO702 polypeptides having conglutinin activity would be expected to be capable of inhibiting haemagglutinin activity by 15 influenza viruses and/or function as immunoglobulin-independent defense molecules as a result of a complement-mediated mechanism.

PRO703 polypeptides of the present invention which possess biological activity related to that of the VLCAS protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO703 polypeptides of the present invention for such purposes.

20 PRO703 polypeptides and portions thereof which have homology to VLCAS may also be useful for *in vivo* therapeutic purposes, as well as for various other applications. The identification of novel VLCAS proteins and related molecules may be relevant to a number of human disorders. Thus, the identification of new VLCAS proteins and VLCAS protein-like molecules is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and 25 medical research as well as various industrial applications. As a result, there is particular scientific and medical interest in new molecules, such as PRO703.

PRO705 polypeptides of the present invention which possess biological activity related to that of the K-glycan protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO705 polypeptides of the present invention for such purposes.

30 PRO708 polypeptides of the present invention which possess biological activity related to that of the aryl sulfatase proteins may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO708 polypeptides of the present invention for such purposes.

35 PRO320 polypeptides of the present invention which possess biological activity related to that of the fibulin protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO320 polypeptides of the present invention for such purposes.

PRO320 polypeptides and portions thereof which have homology to fibulin may also be useful for *in vivo* therapeutic purposes, as well as for various other applications. The identification of novel fibulin proteins and related molecules may be relevant to a number of human disorders such as cancer or those involving connective tissue, attachment molecules and related mechanisms. Thus, the identification of new fibulin proteins and fibulin

protein-like molecules is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and medical research as well as various industrial applications. As a result, there is particular scientific and medical interest in new molecules, such as PRO320.

PRO324 polypeptides of the present invention which possess biological activity related to that of oxidoreductases 5 may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO324 polypeptides of the present invention for such purposes.

PRO351 polypeptides of the present invention which possess biological activity related to that of the prostasin protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO351 polypeptides of the present invention for such purposes.

PRO351 polypeptides and portions thereof which have homology to prostasin may also be useful for *in vivo* 10 therapeutic purposes, as well as for various other applications. The identification of novel prostasin proteins and related molecules may be relevant to a number of human disorders. Thus, the identification of new prostasin proteins and prostasin -like molecules is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and 15 medical research as well as various industrial applications. As a result, there is particular scientific and medical interest in new molecules, such as PRO351.

PRO352 polypeptides of the present invention which possess biological activity related to that of the butyrophilin protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO352 polypeptides of the present invention for such purposes.

PRO381 polypeptides of the present invention which possess biological activity related to that of one or more 20 of the FKPB immunophilin proteins may be employed both *in vivo* for therapeutic purposes and *in vitro*, for example for enhancing immunosuppressant activity and/or for axonal regeneration. Those of ordinary skill in the art will well know how to employ the PRO381 polypeptides of the present invention for such purposes.

PRO386 polypeptides of the present invention which possess biological activity related to that of the beta-2 25 subunit of a sodium channel expressed in mammalian cells may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO386 polypeptides of the present invention for such purposes.

PRO540 polypeptides of the present invention which possess biological activity related to that of the LCAT 30 protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO540 polypeptides of the present invention for such purposes.

PRO615 polypeptides of the present invention which possess biological activity related to that of the synaptogyrin protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO615 polypeptides of the present invention for such purposes.

PRO615 polypeptides and portions thereof which have homology to synaptogyrin may also be useful for *in* 35 *vivo* therapeutic purposes, as well as for various other applications. The identification of novel synaptogyrin proteins and related molecules may be relevant to a number of human disorders. Thus, the identification of new synaptogyrin proteins and synaptogyrin-like molecules is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and medical research as well as various industrial applications. As a result, there is particular

scientific and medical interest in new molecules, such as PRO615.

PRO618 polypeptides of the present invention which possess biological activity related to that of an enteropeptidase may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO618 polypeptides of the present invention for such purposes.

PRO618 polypeptides and portions thereof which have homology to enteropeptidase may also be useful for 5 *in vivo* therapeutic purposes, as well as for various other applications. The identification of novel enteropeptidase proteins and related molecules may be relevant to a number of human disorders. Thus, the identification of new enteropeptidase proteins and enteropeptidase-like molecules is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and medical research as well as various industrial applications. As a result, there is particular 10 scientific and medical interest in new molecules, such as PRO618.

PRO719 polypeptides of the present invention which possess biological activity related to that of the lipoprotein lipase H protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO719 polypeptides of the present invention for such purposes.

PRO724 polypeptides of the present invention which possess biological activity related to that of the human 15 LDL receptor protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO724 polypeptides of the present invention for such purposes.

PRO772 polypeptides of the present invention which possess biological activity related to that of the human A4 protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO772 polypeptides of the present invention for such purposes.

20 PRO852 polypeptides of the present invention which possess biological activity related to that of certain protease protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO852 polypeptides of the present invention for such purposes.

25 PRO853 polypeptides of the present invention which possess biological activity related to that of the reductase protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO853 polypeptides of the present invention for such purposes.

PRO853 polypeptides and portions thereof which have homology to reductase proteins may also be useful for *in vivo* therapeutic purposes, as well as for various other applications. Given that oxygen free radicals and 30 antioxidants appear to play important roles in a number of disease processes, the identification of new reductase proteins and reductase-like molecules is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and medical research as well as various industrial applications. As a result, there is particular scientific and medical interest in new molecules, such as PRO853.

35 PRO860 polypeptides of the present invention which possess biological activity related to that of the neurofascin protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO860 polypeptides of the present invention for such purposes.

PRO860 polypeptides and portions thereof which have homology to neurofascin may also be useful for *in vivo* therapeutic purposes, as well as for various other applications. The identification of novel neurofascin proteins and related molecules may be relevant to a number of human disorders which involve cellular adhesion. Thus, the identification of new neurofascin proteins and neurofascin protein-like molecules is of special importance in that such

proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and medical research as well as various industrial applications. As a result, there is particular scientific and medical interest in new molecules, such as PRO860.

PRO846 polypeptides of the present invention which possess biological activity related to that of the CMRF35 protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO846 polypeptides of the present invention for such purposes.

PRO846 polypeptides and portions thereof which have homology to the CMRF35 protein may also be useful for *in vivo* therapeutic purposes, as well as for various other applications. The identification of novel CMRF35 protein and related molecules may be relevant to a number of human disorders. Thus, the identification of new CMRF35 protein and CMRF35 protein-like molecules is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and medical research as well as various industrial applications. As a result, there is particular scientific and medical interest in new molecules, such as PRO846.

PRO862 polypeptides of the present invention which possess biological activity related to that of the lysozyme protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO862 polypeptides of the present invention for such purposes.

PRO862 polypeptides and portions thereof which have homology to the lysozyme protein may also be useful for *in vivo* therapeutic purposes, as well as for various other applications. The identification of novel lysozyme proteins and related molecules may be relevant to a number of human disorders. Thus, the identification of new lysozymes and lysozyme-like molecules is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and medical research as well as various industrial applications. As a result, there is particular scientific and medical interest in new molecules, such as PRO862.

PRO864 polypeptides of the present invention which possess biological activity related to that of the Wnt-4 protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO864 polypeptides of the present invention for such purposes.

PRO864 polypeptides and portions thereof which have homology to the Wnt-4 protein may also be useful for *in vivo* therapeutic purposes, as well as for various other applications. The identification of novel Wnt-4 proteins and related molecules may be relevant to a number of human disorders. Thus, the identification of new Wnt-4 protein and Wnt-4 protein-like molecules is of special importance in that such proteins may serve as potential therapeutics for a variety of different human disorders. Such polypeptides may also play important roles in biotechnological and medical research as well as various industrial applications. As a result, there is particular scientific and medical interest in new molecules, such as PRO864.

PRO792 polypeptides of the present invention which possess biological activity related to that of the CD23 protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO792 polypeptides of the present invention for such purposes.

PRO866 polypeptides of the present invention which possess biological activity related to that of mindin and/or spondin protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO866 polypeptides of the present invention for such purposes.

PRO871 polypeptides of the present invention which possess biological activity related to that of the cyclophilin protein family may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO871 polypeptides of the present invention for such purposes.

PRO873 polypeptides of the present invention which possess biological activity related to that of carboxylesterases may be employed both *in vivo* for therapeutic purposes and *in vitro*. For example, they be used

- 5 in conjunction with prodrugs to convert the prodrug to its active form (see Danks *et al.*, *supra*). They may be used to inhibit parasite infection (see van Pelt *et al.*, *supra*). Methods for employ the PRO873 polypeptides of the present invention for these, and other purposes will be readily apparent to those of ordinary skill in the art.

PRO940 polypeptides of the present invention which possess biological activity related to that of the CD33 protein and/or OB binding protein-2 may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of

- 10 ordinary skill in the art will well know how to employ the PRO940 polypeptides of the present invention for such purposes.

PRO941 polypeptides of the present invention which possess biological activity related to that of a cadherin protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO941 polypeptides of the present invention for such purposes.

- 15 PRO944 polypeptides of the present invention which possess biological activity related to that of the CPE-R protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO944 polypeptides of the present invention for such purposes. PRO944 polypeptides of the present invention that function to bind to Clostridium perfringens enterotoxin (CPE) may find use for effectively treating infection by the CPE endotoxin.

- 20 PRO983 polypeptides of the present invention which possess biological activity related to that of the vesicle-associated membrane protein, VAP-33, may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO983 polypeptides of the present invention for such purposes.

- 25 PRO1057 polypeptides of the present invention which possess biological activity related to that of protease proteins may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO1057 polypeptides of the present invention for such purposes.

PRO1071 polypeptides of the present invention which possess biological activity related to that of the thrombospondin protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO1071 polypeptides of the present invention for such purposes.

- 30 PRO1072 polypeptides of the present invention which possess biological activity related to that of reductase proteins may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO1072 polypeptides of the present invention for such purposes.

- 35 PRO1075 polypeptides of the present invention which possess biological activity related to that of protein disulfide isomerase may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO1075 polypeptides of the present invention for such purposes.

PRO181 polypeptides of the present invention which possess biological activity related to that of the cornichon protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO181 polypeptides of the present invention for such purposes.

PRO827 polypeptides of the present invention which possess biological activity related to that of various integrin proteins may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO827 polypeptides of the present invention for such purposes.

5 PRO1114 polypeptides of the present invention which possess biological activity related to that of the cytokine receptor family of proteins may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO1114 polypeptides of the present invention for such purposes.

In addition to the above, the PRO1114 interferon receptor polypeptides may be employed in applications, both *in vivo* and *in vitro*, where the ability to bind to an interferon ligand is desired. Such applications will be well within the skill level in the art.

10 PRO237 polypeptides of the present invention which possess biological activity related to that of the carbonic anhydrase protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO237 polypeptides of the present invention for such purposes.

15 PRO541 polypeptides of the present invention which possess biological activity related to that of a trypsin inhibitor protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO541 polypeptides of the present invention for such purposes.

PRO273 polypeptides can be used in assays that other chemokines would be used in to perform comparative assays. The results can be used accordingly.

20 PRO701 polypeptides of the present invention which possess biological activity related to that of the neuroligin family may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO701 polypeptides of the present invention for such purposes.

PRO701 can be used in assays with neurons and its activity thereon can be compared with that of neuroligins 1, 2 and 3. The results can be applied accordingly.

25 PRO704 polypeptides of the present invention which possess biological activity related to that of vesicular integral membrane proteins may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO704 polypeptides of the present invention for such purposes.

PRO704 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly. PRO704 can be tagged or measured for activity to measure endocytosis activity and thereby used to screen for agents which effect endocytosis.

30 PRO706 polypeptides of the present invention which possess biological activity related to that of the endogenous prostatic acid phosphatase precursor may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO706 polypeptides of the present invention for such purposes.

35 PRO706 can be used in assays with human prostatic acid phosphatase or human lysosomal acid phosphatase and its activity thereon can be compared with that of human prostatic acid phosphatase or human lysosomal acid phosphatase. The results can be applied accordingly.

PRO707 polypeptides of the present invention which possess biological activity related to that of cadherins may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO707 polypeptides of the present invention for such purposes.

PRO707 can be used in assays to determine its activity in relation to other cadherins, particularly cadherin FIB3. The results can be applied accordingly.

PRO322 polypeptides of the present invention which possess biological activity related to that of neuropsin may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO322 polypeptides of the present invention for such purposes.

5 PRO322 can be used in assays to determine its activity relative to neuropsin, trypsinogen, serine protease and neurosin, and the results applied accordingly.

PRO526 polypeptides of the present invention which possess biological activity related to that of protein-protein binding proteins may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO526 polypeptides of the present invention for such purposes.

10 Assays can be performed with growth factors and other proteins which are known to form complexes to determine whether PRO526 binds thereto and whether there is increased half-life due to such binding. The results can be used accordingly.

15 PRO531 polypeptides of the present invention which possess biological activity related to that of the protocadherins may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO531 polypeptides of the present invention for such purposes.

PRO531 can be used in assays against protocadherin 3 and other protocadherins, to determine their relative activities. The results can be applied accordingly.

20 PRO534 polypeptides of the present invention which possess biological activity related to that of the protein disulfide isomerase may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO534 polypeptides of the present invention for such purposes.

PRO534 can be used in assays with protein disulfide isomerase to determine the relative activities. The results can be applied accordingly.

25 PRO697 polypeptides of the present invention which possess biological activity related to that of the sFRP family may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO697 polypeptides of the present invention for such purposes.

PRO697 can be used in assays with sFRPs and SARPs to determine the relative activities. The results can be applied accordingly.

30 PRO731 polypeptides of the present invention which possess biological activity related to that of any protocadherin may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO731 polypeptides of the present invention for such purposes.

PRO731 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly.

35 PRO768 polypeptides of the present invention which possess biological activity related to that of integrins may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO768 polypeptides of the present invention for such purposes.

PRO768 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly.

PRO771 polypeptides of the present invention which possess biological activity related to that of the testican protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will

well know how to employ the PRO771 polypeptides of the present invention for such purposes.

PRO771 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly.

PRO733 polypeptides of the present invention which possess biological activity related to that of the proteins which bind the T1/ST2 receptor may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO733 polypeptides of the present invention for such purposes.

PRO733 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly.

PRO162 polypeptides of the present invention which possess biological activity related to that of the pancreatitis-associated protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO162 polypeptides of the present invention for such purposes.

PRO162 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly.

PRO788 polypeptides of the present invention which possess biological activity related to that of the anti-neoplastic urinary protein may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO788 polypeptides of the present invention for such purposes.

PRO788 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly.

PRO1008 polypeptides of the present invention which possess biological activity related to that of dkk-1 may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO1008 polypeptides of the present invention for such purposes.

PRO1008 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly.

PRO1012 polypeptides of the present invention which possess biological activity related to that of the protein disulfide isomerase may be employed both *in vivo* and *in vitro* purposes. Those of ordinary skill in the art will well know how to employ the PRO1012 polypeptides of the present invention for such purposes.

PRO1012 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly.

PRO1014 polypeptides of the present invention which possess biological activity related to that of reductase may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO1014 polypeptides of the present invention for such purposes.

PRO1014 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. Inhibitors of PRO1014 are particularly preferred. The results can be applied accordingly.

PRO1017 polypeptides of the present invention which possess biological activity related to that of sulfotransferase may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO1017 polypeptides of the present invention for such purposes.

PRO1017 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly.

PRO474 polypeptides of the present invention which possess biological activity related to that of dehydrogenase may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO474 polypeptides of the present invention for such purposes.

PRO474 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly.

5 PRO1031 polypeptides of the present invention which possess biological activity related to that of IL-17 may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO1031 polypeptides of the present invention for such purposes.

PRO1031 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly.

10 PRO938 polypeptides of the present invention which possess biological activity related to that of protein disulfide isomerase may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO938 polypeptides of the present invention for such purposes.

15 PRO1082 polypeptides of the present invention which possess biological activity related to that of the LDL receptor may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO1082 polypeptides of the present invention for such purposes.

PRO1082 can be used in assays with the polypeptides to which they have identity with to determine the relative activities. The results can be applied accordingly. PRO1082 can also be used in assays to identify candidate agents which modulate the receptors.

20 PRO1083 polypeptides of the present invention which possess biological activity related to that of 7TM receptors may be employed both *in vivo* for therapeutic purposes and *in vitro*. Those of ordinary skill in the art will well know how to employ the PRO1083 polypeptides of the present invention for such purposes.

In particular PRO1083 can be used in assays to determine candidate agents which control or modulate PRO1083, i.e., have an effect on the receptor.

25 The VEGF-E molecules herein have a number of therapeutic uses associated with survival, proliferation and/or differentiation of cells. Such uses include the treatment of umbilical vein endothelial cells, in view of the demonstrated ability of VEGF-E to increase survival of human umbilical vein endothelial cells. Treatment may be needed if the vein were subjected to traumata, or situations wherein artificial means are employed to enhance the survival of the umbilical vein, for example, where it is weak, diseased, based on an artificial matrix, or in an artificial environment. Other physiological conditions that could be improved based on the selective mitogenic 30 character of VEGF-E are also included herein. Uses also include the treatment of fibroblasts and myocytes, in view of the demonstrated ability of VEGF-E to induce proliferation of fibroblasts and hypertrophy in myocytes. In particular, VEGF-E can be used in wound healing, tissue growth and muscle generation and regeneration.

35 For the indications referred to above, the VEGF-E molecule will be formulated and dosed in a fashion consistent with good medical practice taking into account the specific disorder to be treated, the condition of the individual patient, the site of delivery of the VEGF-E, the method of administration, and other factors known to practitioners. Thus, for purposes herein, the "therapeutically effective amount" of the VEGF-E is an amount that is effective either to prevent, lessen the worsening of, alleviate, or cure the treated condition, in particular that amount which is sufficient to enhance the survival, proliferation and/or differentiation of the treated cells *in vivo*.

VEGF-E amino acid variant sequences and derivatives that are immunologically crossreactive with antibodies raised against native VEGF are useful in immunoassays for VEGF-E as standards, or, when labeled, as competitive reagents.

The VEGF-E is prepared for storage or administration by mixing VEGF-E having the desired degree of purity with physiologically acceptable carriers, excipients, or stabilizers. Such materials are non-toxic to recipients at the dosages and concentrations employed. If the VEGF-E is water soluble, it may be formulated in a buffer such as phosphate or other organic acid salt preferably at a pH of about 7 to 8. If the VEGF-E is only partially soluble in water, it may be prepared as a microemulsion by formulating it with a nonionic surfactant such as Tween, Pluronics, or PEG, e.g., Tween 80, in an amount of 0.04-0.05% (w/v), to increase its solubility.

Optionally other ingredients may be added such as antioxidants, e.g., ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrins; chelating agents such as EDTA; and sugar alcohols such as mannitol or sorbitol.

The VEGF-E to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). The VEGF-E ordinarily will be stored in lyophilized form or as an aqueous solution if it is highly stable to thermal and oxidative denaturation. The pH of the VEGF-E preparations typically will be about from 6 to 8, although higher or lower pH values may also be appropriate in certain instances. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of salts of the VEGF-E.

If the VEGF-E is to be used parenterally, therapeutic compositions containing the VEGF-E generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Generally, where the disorder permits, one should formulate and dose the VEGF-E for site-specific delivery. This is convenient in the case of wounds and ulcers. Sustained release formulations may also be prepared, and include the formation of microcapsular particles and implantable articles. For preparing sustained-release VEGF-E compositions, the VEGF-E is preferably incorporated into a biodegradable matrix or microcapsule. A suitable material for this purpose is a polylactide, although other polymers of poly-(α -hydroxycarboxylic acids), such as poly-D-(-)-3-hydroxybutyric acid (EP 133,988A), can be used. Other biodegradable polymers include poly(lactones), poly(acetals), poly(orthoesters), or poly(orthocarbonates). The initial consideration here must be that the carrier itself, or its degradation products, is nontoxic in the target tissue and will not further aggravate the condition. This can be determined by routine screening in animal models of the target disorder or, if such models are unavailable, in normal animals. Numerous scientific publications document such animal models.

For examples of sustained release compositions, see U.S. Patent No. 3,773,919, EP 58,481A, U.S. Patent No. 3,887,699, EP 158,277A, Canadian Patent No. 1176565, U. Sidman *et al.*, *Biopolymers* 22, 547 [1983], and R. Langer *et al.*, *Chem. Tech.* 12, 98 [1982].

When applied topically, the VEGF-E is suitably combined with other ingredients, such as carriers and/or adjuvants. There are no limitations on the nature of such other ingredients, except that they must be pharmaceutically

acceptable and efficacious for their intended administration, and cannot degrade the activity of the active ingredients of the composition. Examples of suitable vehicles include ointments, creams, gels, or suspensions, with or without purified collagen. The compositions also may be impregnated into transdermal patches, plasters, and bandages, preferably in liquid or semi-liquid form.

For obtaining a gel formulation, the VEGF-E formulated in a liquid composition may be mixed with an effective amount of a water-soluble polysaccharide or synthetic polymer such as polyethylene glycol to form a gel of the proper viscosity to be applied topically. The polysaccharide that may be used includes, for example, cellulose derivatives such as etherified cellulose derivatives, including alkyl celluloses, hydroxyalkyl celluloses, and alkylhydroxyalkyl celluloses, for example, methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl methylcellulose, and hydroxypropyl cellulose; starch and fractionated starch; agar; alginic acid and alginates; gum arabic; pullulan; agarose; carrageenan; dextrans; dextrins; fructans; inulin; mannans; xylans; arabinans; chitosans; glycogens; glucans; and synthetic biopolymers; as well as gums such as xanthan gum; guar gum; locust bean gum; gum arabic; tragacanth gum; and karaya gum; and derivatives and mixtures thereof. The preferred gelling agent herein is one that is inert to biological systems, nontoxic, simple to prepare, and not too runny or viscous, and will not destabilize the VEGF-E held within it.

Preferably the polysaccharide is an etherified cellulose derivative, more preferably one that is well defined, purified, and listed in USP, e.g., methylcellulose and the hydroxyalkyl cellulose derivatives, such as hydroxypropyl cellulose, hydroxyethyl cellulose, and hydroxypropyl methylcellulose. Most preferred herein is methylcellulose.

The polyethylene glycol useful for gelling is typically a mixture of low and high molecular weight polyethylene glycols to obtain the proper viscosity. For example, a mixture of a polyethylene glycol of molecular weight 400-600 with one of molecular weight 1500 would be effective for this purpose when mixed in the proper ratio to obtain a paste.

The term "water soluble" as applied to the polysaccharides and polyethylene glycols is meant to include colloidal solutions and dispersions. In general, the solubility of the cellulose derivatives is determined by the degree of substitution of ether groups, and the stabilizing derivatives useful herein should have a sufficient quantity of such ether groups per anhydroglucosidic unit in the cellulose chain to render the derivatives water soluble. A degree of ether substitution of at least 0.35 ether groups per anhydroglucosidic unit is generally sufficient. Additionally, the cellulose derivatives may be in the form of alkali metal salts, for example, the Li, Na, K, or Cs salts.

If methylcellulose is employed in the gel, preferably it comprises about 2-5%, more preferably about 3% of the gel and the VEGF is present in an amount of about 300-1000 mg per ml of gel.

The dosage to be employed is dependent upon the factors described above. As a general proposition, the VEGF-E is formulated and delivered to the target site or tissue at a dosage capable of establishing in the tissue a VEGF-E level greater than about 0.1 ng/cc up to a maximum dose that is efficacious but not unduly toxic. This intra-tissue concentration should be maintained if possible by continuous infusion, sustained release, topical application, or injection at empirically determined frequencies.

It is within the scope hereof to combine the VEGF-E therapy with other novel or conventional therapies (e.g., growth factors such as VEGF, aFGF, bFGF, PDGF, IGF, NGF, anabolic steroids, EGF or TGF-a) for enhancing the activity of any of the growth factors, including VEGF-E, in promoting cell proliferation, survival, differentiation and repair. It is not necessary that such cotreatment drugs be included per se in the compositions of this invention, although this will be convenient where such drugs are proteinaceous. Such admixtures are suitably

administered in the same manner and for the same purposes as the VEGF-E used alone. The useful molar ratio of VEGF-E to such secondary growth factors is typically 1:0.1-10, with about equimolar amounts being preferred.

The compounds of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the PRO polypeptide hereof is combined in admixture with a pharmaceutically acceptable carrier vehicle. Suitable carrier vehicles and their formulation, inclusive of other human proteins, e.g., human serum albumin, are described, for example, in *Remington's Pharmaceutical Sciences*, 16th ed., 1980, Mack Publishing Co., edited by Oslo *et al.* the disclosure of which is hereby incorporated by reference. The VEGF-E herein may be administered parenterally to subjects suffering from cardiovascular diseases or conditions, or by other methods that ensure its delivery to the bloodstream in an effective form.

Compositions particularly well suited for the clinical administration of VEGF-E hereof employed in the practice of the present invention include, for example, sterile aqueous solutions, or sterile hydratable powders such as lyophilized protein. It is generally desirable to include further in the formulation an appropriate amount of a pharmaceutically acceptable salt, generally in an amount sufficient to render the formulation isotonic. A pH regulator such as arginine base, and phosphoric acid, are also typically included in sufficient quantities to maintain an appropriate pH, generally from 5.5 to 7.5. Moreover, for improvement of shelf-life or stability of aqueous formulations, it may also be desirable to include further agents such as glycerol. In this manner, variant t-PA formulations are rendered appropriate for parenteral administration, and, in particular, intravenous administration.

Dosages and desired drug concentrations of pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. For example, in the treatment of deep vein thrombosis or peripheral vascular disease, "bolus" doses, will typically be preferred with subsequent administrations being given to maintain an approximately constant blood level, preferably on the order of about 3 $\mu\text{g}/\text{ml}$.

However, for use in connection with emergency medical care facilities where infusion capability is generally not available and due to the generally critical nature of the underlying disease (e.g., embolism, infarct), it will generally be desirable to provide somewhat larger initial doses, such as an intravenous bolus.

For the various therapeutic indications referred to for the compounds hereof, the VEGF-E molecules will be formulated and dosed in a fashion consistent with good medical practice taking into account the specific disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners in the respective art. Thus, for purposes herein, the "therapeutically effective amount" of the VEGF-E molecules hereof is an amount that is effective either to prevent, lessen the worsening of, alleviate, or cure the treated condition, in particular that amount which is sufficient to enhance the survival, proliferation or differentiation of targeted cells *in vivo*. In general a dosage is employed capable of establishing in the tissue that is the target for the therapeutic indication being treated a level of a VEGF-E hereof greater than about 0.1 ng/cm^3 up to a maximum dose that is efficacious but not unduly toxic. It is contemplated that intra-tissue administration may be the choice for certain of the therapeutic indications for the compounds hereof.

The human Toll proteins of the present invention can also be used in assays to identify other proteins or molecules involved in Toll-mediated signal transduction. For example, PRO285 and PRO286 are useful in identifying the as of yet unknown natural ligands of human Tolls, or other factors that participate (directly or indirectly) in the activation of and/or signaling through a human Toll receptor, such as potential Toll receptor associated kinases. In addition, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Screening assays can be designed to find lead compounds that mimic the biological activity of a native Toll polypeptide or a ligand for a native Toll polypeptide. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

5 *In vitro* assays employ a mixture of components including a Toll receptor polypeptide, which may be part of fusion product with another peptide or polypeptide, e.g., a tag for detecting or anchoring, etc. The assay mixtures may further comprise (for binding assays) a natural intra- or extracellular Toll binding target (i.e. a Toll ligand, or another molecule known to activate and/or signal through the Toll receptor). While native binding targets may be used, it is frequently preferred to use portion of such native binding targets (e.g. peptides), so long as the portion provides binding affinity and avidity to the subject Toll protein conveniently measurable in the assay. The assay 10 mixture also contains a candidate pharmacological agent. Candidate agents encompass numerous chemical classes, through typically they are organic compounds, preferably small organic compounds, and are obtained from a wide variety of sources, including libraries of synthetic or natural compounds. A variety of other reagents may also be included in the mixture, such as, salts, buffers, neutral proteins, e.g. albumin, detergents, protease inhibitors, 15 nuclease inhibitors, antimicrobial agents, etc.

In *in vitro* binding assays, the resultant mixture is incubated under conditions whereby, but for the presence of the candidate molecule, the Toll protein specifically binds the cellular binding target, portion or analog, with a reference binding affinity. The mixture components can be added in any order that provides for the requisite bindings 20 and incubations may be performed at any temperature which facilitates optimal binding. Incubation periods are likewise selected for optimal binding but also minimized to facilitate rapid high-throughput screening.

After incubation, the agent-biased binding between the Toll protein and one or more binding targets is detected by any convenient technique. For cell-free binding type assays, a separation step is often used to separate bound from unbound components. Separation may be effected by precipitation (e.g. TCA precipitation, 25 immunoprecipitation, etc.), immobilization (e.g. on a solid substrate), etc., followed by washing by, for example, membrane filtration (e.g. Whatman's P-18 ion exchange paper, Polyfiltronic's hydrophobic GFC membrane, etc.), gel chromatography (e.g. gel filtration, affinity, etc.). For Toll-dependent transcription assays, binding is detected by a change in the expression of a Toll-dependent reporter.

Detection may be effected in any convenient way. For cell-free binding assays, one of the components 30 usually comprises or is coupled to a label. The label may provide for direct detection as radioactivity, luminescence, optical or electron density, etc., or indirect detection, such as, an epitope tag, an enzyme, etc. A variety of methods may be used to detect the label depending on the nature of the label and other assay components, e.g. through optical or electron density, radiative emissions, nonradiative energy transfers, etc. or indirectly detected with antibody conjugates, etc.

35 Nucleic acid encoding the Toll polypeptides disclosed herein may also be used in gene therapy. In gene therapy applications, genes are introduced into cells in order to achieve *in vivo* synthesis of a therapeutically effective genetic product, for example for replacement of a defective gene. "Gene therapy" includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA. Antisense

RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has already been shown that short antisense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane. (Zamecnik *et al.*, Proc. Natl. Acad. Sci. USA **83**, 4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e.g. by substituting their negatively charged phosphodiester groups by uncharged groups.

5 There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically retroviral) 10 vectors and viral coat protein-liposome mediated transfection (Dzau *et al.*, Trends in Biotechnology **11**, 205-210 [1993]). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for 15 a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu *et al.*, J. Biol. Chem. **262**, 4429-4432 (1987); and Wagner *et al.*, Proc. Natl. Acad. Sci. USA **87**, 3410-3414 (1990). For review of the currently known gene marking and gene therapy protocols see Anderson *et al.*, Science **256**, 808-813 (1992).

20 The various uses listed in connection with the Toll proteins herein, are also available for agonists of the native Toll receptors, which mimic at least one biological function of a native Toll receptor.

Neurotrimin as well as other members of the IgLON subfamily of the immunoglobulin superfamily have been identified to have effect upon neural patterning, differentiation, maturation and growth. As a result, PRO337 25 the human neurotrimin homolog polypeptides would be expected to have utility in diseases which are characterized by neural dysfunction. For example, motoneuron disorders such as amyotrophic lateral sclerosis (Lou Gehrig's disease), Bell's palsy, and various conditions involving spinal muscular atrophy, or paralysis. NGF variant formulations of the invention can be used to treat human neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, Huntington's chorea, Down's Syndrome, nerve deafness, and Meniere's disease. Moreover PRO337 polypeptide may also be used as a cognitive enhancer, to enhance learning 30 particularly in dementia or trauma, such as those associated with the above diseases.

Further, PRO337 may be employed to treat neuropathy, and especially peripheral neuropathy. "Peripheral neuropathy" refers to a disorder affecting the peripheral nervous system, most often manifested as one or a combination of motor, sensory, sensorimotor, or autonomic neural dysfunction. The wide variety of morphologies exhibited by peripheral neuropathies can each be attributed uniquely to an equally wide number of causes. For 35 example, peripheral neuropathies can be genetically acquired, can result from a systemic disease, or can be induced by a toxic agent. Examples include but are not limited to diabetic peripheral neuropathy, distal sensorimotor neuropathy, or autonomic neuropathies such as reduced motility of the gastrointestinal tract or atony of the urinary bladder. Examples of neuropathies associated with systemic disease include post-polio syndrome or AIDS-associated neuropathy; examples of hereditary neuropathies include Charcot-Marie-Tooth disease, Refsum's disease,

Abetalipoproteinemia, Tangier disease, Krabbe's disease, Metachromatic leukodystrophy, Fabry's disease, and Dejerine-Sottas syndrome; and examples of neuropathies caused by a toxic agent include those caused by treatment with a chemotherapeutic agent such as vincristine, cisplatin, methotrexate, or 3'-azido-3'-deoxythymidine. Correspondingly, neurotrimin antagonists would be expected to have utility in diseases characterized by excessive neuronal activity.

5 Endothelin is generated from inactive intermediates, the big endothelins, by a unique processing event catalyzed by the zinc metalloprotease, endothelin converting enzyme (ECE). ECE was recently cloned, and its structure was shown to be a single pass transmembrane protein with a short intracellular N-terminal and a long extracellular C-terminal that contains the catalytic domain and numerous N-glycosylation sites. ECEs cleave the endothelin propeptide between Trp73 and Val74 producing the active peptide, ET, which appears to function as a
10 local rather than a circulating hormone (Rubanyi, G.M. & Polokoff, M.A., *Pharmacological Reviews* 46: 325-415 (1994). Thus ECE activity is a potential site of regulation of endothelin production and a possible target for therapeutic intervention in the endothelin system. By blocking ECE activity, it is possible stop the production of ET-1 by inhibiting the conversion of the relatively inactive precursor, big ET-1, to the physiologically active form.

ECE-2 is 64% identical to bovine ECE-2 at the amino acid level. ECE-2 is closely related to ECE-1 (63%
15 identical, 80% conserved), neutral endopeptidase 24.11 and the Kell blood group protein. Bovine ECE-2 is a type II membrane-bound metalloproteinase localized in the trans-Golgi network where it acts as an intracellular enzyme converting endogenous big endothelin-1 into active endothelin (Emoto, N. and Yanagisawa, M., *J. Biol. Chem.* 270: 15262-15268 (1995). The bovine ECE-2 mRNA expression is highest in parts of the brain, cerebral cortex, cerebellum and adrenal medulla. It is expressed at lower levels in myometrium, testes, ovary, and endothelial cells.
20 Bovine ECE-2 and ECE-1 both are more active on ET-1 as a substrate compared to ET-2 or ET-3, Emoto and Yanangisawa, supra.

Human ECE-2 is 736 amino acids in length with a 31 residue amino-terminal tail, a 23 residue transmembrane helix and a 682 carboxy-terminal domain. It is 94% identical to bovine ECE-2 and 64% identical to human ECE-1. The predicted transmembrane domain is highly conserved between the human and bovine ECE-2 proteins and between
25 human ECE-1 and human ECE-2, as are the putative N-linked glycosylation sites, Cys residues conserved in the neutral endopeptidase 24.11 and the Kell blood group protein family and the putative zinc binding motif. The sequence suggests, that like other members of the NEP-ECE-Kell family, human ECE-2 encodes a type II transmembrane zinc-binding metalloproteinase, which, by extrapolation from what is known about bovine ECE-2, is an intracellular enzyme located within the secretory pathway which processes endogenously produced big ET-1
30 while it is still in the secretory vesicles. Emoto and Yanangisawa, supra.

The expression pattern of ECE-2 differs from that observed for ECE-1. Northern blot analysis of mRNA levels indicated low levels of expression of a 3.3 kb transcript in adult brain (highest in the cerebellum, putamen, medulla and temporal lobe, and lower in the cerebral cortex, occipital lobe and frontal lobe), spinal cord, lung and pancreas and higher levels of a 4.5 kb transcript in fetal brain and kidney. The two transcript sizes probably
35 represent the use of alternative polyadenylation sites as has been observed for bovine ECE-2 (Emoto and Yanangisawa, supra) and ECE-1 (Xu et al., *Cell* 78: 473-485 (1994)). PCR on cDNA libraries indicated low levels of expression in fetal brain, fetal kidney, fetal small intestine and adult testis. Fetal liver, fetal lung and adult pancreas were all negative.

The endothelin (ET) family of peptides have potent vascular, cardiac and renal actions which may be of pathophysiological importance in many human disease states. ET-1 is expressed as an inactive 212 amino acid prepropeptide. The prepropeptide is first cleaved at Arg52-Cys53 and Arg92-Ala93 and then the carboxy terminal Lys91 and Arg92 are trimmed from the protein to generate the propeptide big ET-1. ECEs then cleave the propeptide between Trp73 and Val74, producing the active peptide, ET, which appears to function as a local rather than a 5 circulating hormone (Rubanyi and Polokoff, *Pharma. R.* 46: 325-415 (1994)).

Endothelins may play roles in the pathophysiology of a number of disease states including: 1) cardiovascular diseases (vasospasm, hypertension, myocardial ischemia; reperfusion injury and acute myocardial infarction, stroke (cerebral ischemia), congestive heart failure, shock, atherosclerosis, vascular thickening); 2) kidney disease (acute and chronic renal failure, glomerulonephritis, cirrhosis); 3) lung disease (bronchial asthma, pulmonary hypertension); 10 4) gastrointestinal disorders (gastric ulcer, inflammatory bowel diseases); 5) reproductive disorders (premature labor, dysmenorrhea, preeclampsia) and 6) carcinogenesis. Rubanyi & Polokoff, *supra*.

Diseases can be evaluated for the impact of ET upon them by examining: 1) increased production of ETs; 2) increased reactivity to ETs; and/or 3) efficacy of an ET receptor antagonist, antibody or ECE inhibitor. Response to the previous criteria suggest that ETs likely play roles in cerebral vasospasm following subarachnoid hemorrhage, 15 hypertension (fulminant/complications), acute renal failure and congestive heart failure. While inhibitors of ET production or activity have not been used in models of coronary vasospasm, acute myocardial infarction, and atherosclerosis, they do have elevated ET levels and increase reactivity to ETs. Shock and pulmonary hypertension also exhibit elevated ET levels (Rubanyi and Polokoff, *supra*). Inhibition of ECEs in these conditions may be of therapeutic value.

20 The expression pattern of ECE-2 differs from that observed for ECE-1. ECE-2 was observed at low levels in the adult brain, lung and pancreas and higher levels in fetal brain and kidney by Northern blot analysis (Fig. 8). PCR revealed low levels of expression in additional tissues: fetal lung, fetal small intestine and adult testis. Fetal liver was negative. A similar pattern was reported for bovine ECE-2 (Emoto and Yanagisawa, *supra*). It is expressed in brain tissues (cerebral cortex, cerebellum and adrenal medulla), myometrium and testis, and in low levels in ovary and very 25 low levels in many other tissues. Bovine ECE-1 (Xu et al, *supra*) is more widely and more abundantly expressed. It is observed in vascular endothelial cells of most organs and in some parenchymal cells. With the exception for brain, bovine ECE-2 mRNA was present at lower levels than ECE-1. Applicants believe ECE-2 to be a particularly good target for the therapeutic intervention for diseases such as cerebral vasospasm following subarachnoid hemorrhage and stroke.

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92. Anti-PRO Polypeptide Antibodies

The present invention further provides anti-PRO polypeptide antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

35

A. Polyclonal Antibodies

The anti-PRO polypeptide antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent

may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be
5 selected by one skilled in the art without undue experimentation.

B. Monoclonal Antibodies

The anti-PRO polypeptide antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, *Nature*, 256:495 (1975).
10 In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the PRO polypeptide of interest or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells
15 or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103]. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that
20 preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of
25 antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Rockville, Maryland. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur *et al.*, *Monoclonal Antibody
30 Production Techniques and Applications*, Marcel Dekker, Inc., New York, (1987) pp. 51-63].

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the PRO polypeptide of interest. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques
35 and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, *Anal. Biochem.*, 107:220 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Goding, *supral*]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown

in vivo as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in 5 U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells 10 that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent No. 4,816,567; Morrison et al., *supra*] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the 15 constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified 20 heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

25

C. Humanized Antibodies

The anti-PRO polypeptide antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂, or other antigen-binding subsequences 30 of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also 35 comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., *Nature*, 321: 522-525 (1986); Riechmann et al.,

Nature, 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.*, 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones *et al.*, *Nature*, 321: 5 522-525 (1986); Riechmann *et al.*, *Nature*, 332:323-327 (1988); Verhoeyen *et al.*, *Science*, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR 10 residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, *J. Mol. Biol.*, 227:381 (1991); Marks *et al.*, *J. Mol. Biol.*, 222:581 (1991)]. The techniques of Cole *et al.* and Boerner *et al.* are also available for the preparation of human monoclonal antibodies (Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985) and Boerner *et al.*, *J. Immunol.*, 15 147(1):86-95 (1991)].

D. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO 20 polypeptide, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities [Milstein and Cuello, *Nature*, 305:537-539 (1983)]. Because of the 25 random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, *EMBO J.*, 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be 30 fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted 35 into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh *et al.*, *Methods in Enzymology*, 121:210 (1986).

E. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target

immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptopbutyrimidate and those disclosed, for example, in U.S. 5 Patent No. 4,676,980.

93. Uses for Anti-PRO Polypeptide Antibodies

The anti-PRO polypeptide antibodies of the invention have various utilities. For example, anti-PRO polypeptide antibodies may be used in diagnostic assays for a PRO polypeptide, *e.g.*, detecting its expression in 10 specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases [Zola, *Monoclonal Antibodies: A Manual of Techniques*, CRC Press, Inc. (1987) pp. 147-158]. The antibodies used in the diagnostic assays can be labeled with a detectable moiety. The 15 detectable moiety should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I , a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase. Any method known in the art for conjugating the antibody to the 20 detectable moiety may be employed, including those methods described by Hunter *et al.*, *Nature*, 144:945 (1962); David *et al.*, *Biochemistry*, 13:1014 (1974); Pain *et al.*, *J. Immunol. Meth.*, 40:219 (1981); and Nygren, *J. Histochem. and Cytochem.*, 30:407 (1982).

Anti-PRO polypeptide antibodies also are useful for the affinity purification of PRO polypeptide from recombinant cell culture or natural sources. In this process, the antibodies against the PRO polypeptide are immobilized on a suitable support, such as Sephadex resin or filter paper, using methods well known in the art. The 25 immobilized antibody then is contacted with a sample containing the PRO polypeptide to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the PRO polypeptide, which is bound to the immobilized antibody. Finally, the support is washed with another suitable solvent that will release the PRO polypeptide from the antibody.

Anti-Toll receptor (*i.e.*, anti-PRO285 and anti-PRO286 antibodies) may also be useful in blocking the 30 biological activities of the respective Toll receptors. The primary function of the family of Toll receptors is believed to be to act as pathogen pattern recognition receptors sensing the presence of conserved molecular pattern present on microbes. Lipopolysaccharides (LPS, also known as endotoxins), potentially lethal molecules produced by various bacteria, bind to the lipopolysaccharide binding protein (LBP) in the blood. The complex formed then activates a receptor known as CD14. There is no consensus in the art about what happens next. According to a hypothesis, CD14 does not directly instruct macrophages to produce cytokines, cell adhesion proteins and enzymes 35 involved in the production of lower molecular weight proinflammatory mediators, rather enables LPS to activate a second receptor. Alternatively, it has been suggested that LPS may activate certain receptors directly, without help from LBP or CD14. The data disclosed in the present application indicate that the human toll-like receptors are signaling receptors that are activated by LPS in an LBP and CD14 responsive manner. As this mechanism, under pathophysiologic conditions can lead to an often fatal syndrome called septic shock, anti-Toll receptor antibodies (just

as other Toll receptor antagonists) might be useful in the treatment of septic shock. It is foreseen that the different Toll receptors might recognize different pathogens, e.g., various strains of Gram-negative or Gram-positive bacteria. Accordingly, in certain situations, combination therapy with a mixture of antibodies specifically binding different Toll receptors, or the use of bispecific anti-Toll antibodies may be desirable.

It is specifically demonstrated that anti-huTLR2 antibodies are believed to be specifically useful in blocking
5 the induction of this receptor by LPS. As it has been shown that LPS exposure can lead to septic shock (Parrillo, N. Engl. J. Med. 328, 1471-1477 [1993]), anti-huTLR2 antibodies are potentially useful in the treatment of septic shock.

The foregoing therapeutic and diagnostic uses listed in connection with the anti-Toll receptor antibodies are also applicable to other Toll antagonists, i.e., other molecules (proteins, peptides, small organic molecules, etc.) that
10 block Toll receptor activation and/or signal transduction mediated by Toll receptors.

In view of their therapeutic potentials, the Toll proteins (including variants of the native Toll homologues), and their agonists and antagonists (including but not limited to anti-Toll antibodies) are incorporated in compositions suitable for therapeutic use. Therapeutic compositions are prepared for storage by mixing the active ingredient having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers
15 (Remington's Pharmaceutical Sciences 16th Edition, Osol, A. Ed. 1980) in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as Tween, Pluronics or PEG.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, supra.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution.

30 Therapeutic compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

The route of administration is in accord with known methods, e.g. injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration, or by sustained release systems.

35 Suitable examples of sustained release preparations include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules. Sustained release matrices include polyesters, hydrogels, polylactides (U.S. Patent 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (U. Sidman *et al.*, Biopolymers 22 (1): 547-556 [1983]), poly (2-hydroxyethyl-methacrylate) (R. Langer, *et al.*, J. Biomed. Mater. Res. 15: 167-277 [1981] and R. Langer, Chem. Tech. 12: 98-105 [1982]), ethylene vinyl acetate

(R. Langer *et al.*, Id.) or poly-D-(*l*)-3-hydroxybutyric acid (EP 133,988). Sustained release compositions also include liposomes. Liposomes containing a molecule within the scope of the present invention are prepared by methods known *per se*: DE 3,218,121; Epstein *et al.*, Proc. Natl. Acad. Sci. USA 82: 3688-3692 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA 77: 4030-4034 (1980); EP 52322; EP 36676A; EP 88046; EP 143949; EP 142641; Japanese patent application 83-118008; U.S. patents 4,485,045 and 4,544,545; and EP 102,324. Ordinarily the 5 liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. % cholesterol, the selected proportion being adjusted for the optimal NT-4 therapy.

An effective amount of the active ingredient will depend, for example, upon the therapeutic objectives, the route of administration, and the condition of the patient. Accordingly, it will be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. A typical daily 10 dosage might range from about 1 $\mu\text{g}/\text{kg}$ to up to 100 mg/kg or more, depending on the factors mentioned above. Typically, the clinician will administer a molecule of the present invention until a dosage is reached that provides the required biological effect. The progress of this therapy is easily monitored by conventional assays.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

15 All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's 20 instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Rockville, Maryland.

EXAMPLE 1: Extracellular Domain Homology Screening to Identify Novel Polypeptides and cDNA Encoding Therefor

25 The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (e.g., Dayhoff, GenBank), and proprietary databases (e.g. LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul and Gish, Methods in Enzymology 266: 460-480 (1996)) as a comparison of the ECD protein sequences 30 to a 6 frame translation of the EST sequences. Those comparisons with a Blast score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, WA; (<http://bozeman.mbt.washington.edu/phrap.docs/phrap.html>)).

Using this extracellular domain homology screen, consensus DNA sequences were assembled relative to 35 the other identified EST sequences using phrap. In addition, the consensus DNA sequences obtained were often (but not always) extended using repeated cycles of BLAST and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above.

Based upon the consensus sequences obtained as described above, oligonucleotides were then synthesized and used to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate

a clone of the full-length coding sequence for a PRO polypeptide. Forward (.f) and reverse (.r) PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe (.p) sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

EXAMPLE 2: Isolation of cDNA clones by Amylase Screening

15 1. Preparation of oligo dT primed cDNA library

mRNA was isolated from a human tissue of interest using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System). In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the SalI/NotI linker cDNA was cloned into XhoI/NotI cleaved vector. pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

20 2. Preparation of random primed cDNA library

A secondary cDNA library was generated in order to preferentially represent the 5' ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY.0 using reagents and protocols from Life Technologies (Super Script Plasmid System, referenced above). In this procedure the double stranded cDNA was sized to 500-1000 bp, linker with blunt to NotI adaptors, cleaved with SfiI, and cloned into SfiI/NotI cleaved vector. pSST-AMY.0 is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with amylase sequence will lead to the secretion of amylase from appropriately transfected yeast colonies.

25 3. Transformation and Detection

DNA from the library described in paragraph 2 above was chilled on ice to which was added electrocompetent DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was added and the mixture was incubated at 37°C for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours (37°C). Positive colonies were scraped off the plates

and the DNA was isolated from the bacterial pellet using standard protocols, e.g. CsCl-gradient. The purified DNA was then carried on to the yeast protocols below.

The yeast methods were divided into three categories: (1) Transformation of yeast with the plasmid/cDNA combined vector; (2) Detection and isolation of yeast clones secreting amylase; and (3) PCR amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

5 The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype: MAT alpha, ura3-52, leu2-3, leu2-112, his3-11, his3-15, MAL⁺, SUC⁺, GAL⁺. Preferably, yeast mutants can be employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles in sec71, sec72, sec62, with truncated sec71 being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins implicated in this post translation 10 pathway (e.g., SEC61p, SEC72p, SEC62p, SEC63p, TDJ1p or SSA1p-4p) or the complex formation of these proteins may also be preferably employed in combination with the amylase-expressing yeast.

15 Transformation was performed based on the protocol outlined by Gietz et al., *Nucl. Acid. Res.*, 20:1425 (1992). Transformed cells were then inoculated from agar into YEPD complex media broth (100 ml) and grown overnight at 30°C. The YEPD broth was prepared as described in Kaiser et al., *Methods in Yeast Genetics*, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 207 (1994). The overnight culture was then diluted to about 2 x 10⁶ cells/ml (approx. OD₆₀₀=0.1) into fresh YEPD broth (500 ml) and regrown to 1 x 10⁷ cells/ml (approx. OD₆₀₀=0.4-0.5).

20 The cells were then harvested and prepared for transformation by transfer into GS3 rotor bottles in a Sorval GS3 rotor at 5,000 rpm for 5 minutes, the supernatant discarded, and then resuspended into sterile water, and 25 centrifuged again in 50 ml falcon tubes at 3,500 rpm in a Beckman GS-6KR centrifuge. The supernatant was discarded and the cells were subsequently washed with LiAc/TE (10 ml, 10 mM Tris-HCl, 1 mM EDTA pH 7.5, 100 mM Li₂OOCCH₃), and resuspended into LiAc/TE (2.5 ml).

Transformation took place by mixing the prepared cells (100 µl) with freshly denatured single stranded salmon testes DNA (Lofstrand Labs, Gaithersburg, MD) and transforming DNA (1 µg, vol. < 10 µl) in microfuge tubes. The mixture was mixed briefly by vortexing, then 40% PEG/TE (600 µl, 40% polyethylene glycol-4000, 10 mM Tris-HCl, 1 mM EDTA, 100 mM Li₂OOCCH₃, pH 7.5) was added. This mixture was gently mixed and incubated at 30°C while agitating for 30 minutes. The cells were then heat shocked at 42°C for 15 minutes, and the reaction vessel centrifuged in a microfuge at 12,000 rpm for 5-10 seconds, decanted and resuspended into TE (500 µl, 10 mM Tris-HCl, 1 mM EDTA pH 7.5) followed by recentrifugation. The cells were then diluted into TE (1 ml) 30 and aliquots (200 µl) were spread onto the selective media previously prepared in 150 mm growth plates (VWR).

Alternatively, instead of multiple small reactions, the transformation was performed using a single, large scale reaction, wherein reagent amounts were scaled up accordingly.

35 The selective media used was a synthetic complete dextrose agar lacking uracil (SCD-Ura) prepared as described in Kaiser et al., *Methods in Yeast Genetics*, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 208-210 (1994). Transformants were grown at 30°C for 2-3 days.

The detection of colonies secreting amylase was performed by including red starch in the selective growth media. Starch was coupled to the red dye (Reactive Red-120, Sigma) as per the procedure described by Biely et al., *Anal. Biochem.*, 172:176-179 (1988). The coupled starch was incorporated into the SCD-Ura agar plates at a final concentration of 0.15% (w/v), and was buffered with potassium phosphate to a pH of 7.0 (50-100 mM final

concentration).

The positive colonies were picked and streaked across fresh selective media (onto 150 mm plates) in order to obtain well isolated and identifiable single colonies. Well isolated single colonies positive for amylase secretion were detected by direct incorporation of red starch into buffered SCD-Ura agar. Positive colonies were determined by their ability to break down starch resulting in a clear halo around the positive colony visualized directly.

5

4. Isolation of DNA by PCR Amplification

When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water (30 μ l) in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5 μ l) was used as a template for the PCR reaction in a 25 μ l volume containing: 0.5 μ l Klentaq (Clontech, Palo Alto, CA); 4.0 μ l 10 mM dNTP's (Perkin Elmer-Cetus); 2.5 μ l Kentaq buffer (Clontech); 0.25 μ l forward oligo 1; 0.25 μ l reverse oligo 2; 12.5 μ l distilled water. The sequence of the forward oligonucleotide 1 was:

5'-TGTAAAACGACGCCAGTAAATAGACCTGCAATTATTAATCT-3' (SEQ ID NO:324)

The sequence of reverse oligonucleotide 2 was:

15 5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAAATCCATT-3' (SEQ ID NO:325)

PCR was then performed as follows:

a.		Denature	92°C, 5 minutes
20 b.	3 cycles of:	Denature	92°C, 30 seconds
		Anneal	59°C, 30 seconds
		Extend	72°C, 60 seconds
25 c.	3 cycles of:	Denature	92°C, 30 seconds
		Anneal	57°C, 30 seconds
		Extend	72°C, 60 seconds
30 d.	25 cycles of:	Denature	92°C, 30 seconds
		Anneal	55°C, 30 seconds
		Extend	72°C, 60 seconds
e.		Hold	4°C

The underlined regions of the oligonucleotides annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY.0 when no insert was present. Typically, 35 the first 18 nucleotides of the 5' end of these oligonucleotides contained annealing sites for the sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (5 μ l) was examined by agarose gel electrophoresis in a 1% agarose gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook et al., *supra*. Clones 40 resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

EXAMPLE 3: Isolation of cDNA Clones Encoding Human PRO213

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA28735. Based on the DNA28735 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO213.

5 A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-TGGAGCAGCAATATGCCAGCC-3' (SEQ ID NO:3)

reverse PCR primer 5'-TTTCACACTCCTGTCGGGTTGG-3' (SEQ ID NO:4)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA28735 sequence which had the following nucleotide sequence

10 hybridization probe

5'-GGTGACACTGCCAGTCAGATGTGGATGAATGCAGTGCTAGGAGGG-3' (SEQ ID NO:5)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO213 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of 15 the cDNA libraries was isolated from human fetal lung tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO213 [herein designated as UNQ187 (DNA30943-1163)] (SEQ ID NO:1) and the derived protein sequence for PRO213.

The entire nucleotide sequence of UNQ187 (DNA30943-1163) is shown in Figure 1 (SEQ ID NO:1). Clone UNQ187 (DNA30943-1163) contains a single open reading frame with an apparent translational initiation site at 20 nucleotide positions 336-338 and ending at the stop codon at nucleotide positions 1221-1223 (Figure 1). The predicted polypeptide precursor is 295 amino acids long (Figure 2). Clone UNQ187 (DNA30943-1163) has been deposited with ATCC.

Analysis of the amino acid sequence of the full-length PRO213 polypeptide suggests that a portion of it possesses significant homology to the human growth arrest-specific gene 6 protein. More specifically, an analysis 25 of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO213 amino acid sequence and the following Dayhoff sequences, HSMHC3W5A_6 and B48089.

EXAMPLE 4: Isolation of cDNA Clones Encoding Human PRO274

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, 30 wherein the consensus sequence obtained is herein designated DNA36469. Based on the DNA36469 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO274. ESTs proprietary to Genentech were employed in the consensus assembly. The ESTs are shown in Figures 5-7 and are herein designated DNA17873, DNA36157 and DNA28929, respectively.

35 Pairs of PCR primers (forward and reverse) were synthesized:

forward PCR primer 1 (36469.f1) 5'-CTGATCCGGTTCTGGTCCCCCTG-3' (SEQ ID NO:11)

forward PCR primer 2 (36469.f2) 5'-GCTCTGTCACTCACGCTC-3' (SEQ ID NO:12)

forward PCR primer 3 (36469.f3) 5'-TCATCTCTCCCTCTCCC-3' (SEQ ID NO:13)

forward PCR primer 4 (36469.f4) 5'-CCTTCCGCCACGGAGTTC-3' (SEQ ID NO:14)

reverse PCR primer 1 (36469_r1) 5'-GGCAAAGTCCACTCCGATGATGTC-3' (SEQ ID NO:15)

reverse PCR primer 2 (36469_r2) 5'-GCCTGCTGTGGTCACAGGTCTCCG-3' (SEQ ID NO:16)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA36469 sequence which had the following nucleotide sequence

hybridization probe (36469_p1)

5 5'-TCGGGGAGCAGGCCATTGAACCGGGGCATTGCTGCTGTCAAGGAGG-3' (SEQ ID NO:17)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO274 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver tissue (LIB229).

10 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO274 [herein designated as UNQ241 (DNA39987-1184)] (SEQ ID NO:1) and the derived protein sequence for PRO274.

The entire nucleotide sequence of UNQ241 (DNA39987-1184) is shown in Figure 3 (SEQ ID NO:6). Clone UNQ241 (DNA39987-1184) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 83-85 and ending at the stop codon at nucleotide positions 1559-1561 (Figure 3). The predicted 15 polypeptide precursor is 492 amino acids long (Figure 4), has an estimated molecular weight of about 54,241 daltons and an estimated pI of about 8.21. Clone UNQ241 (DNA39987-1184) has been deposited with ATCC and is assigned ATCC deposit no. 209786.

Analysis of the amino acid sequence of the full-length PRO274 polypeptide suggests that it possesses significant homology to the Fn54 protein. More specifically, an analysis of the Dayhoff database (version 35.45 20 SwissProt 35) evidenced significant homology between the PRO274 amino acid sequence and the following Dayhoff sequences, MMFN54S2_1, MMFN54S1_1, CELF48C1_8, CEF38B7_6, PRP3_RAT, INL3_PIG, MTCY07A7_13, YNAX_KLEAE, A47234 and HME2_MOUSE.

EXAMPLE 5: Isolation of cDNA Clones Encoding Human PRO300

25 A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA35930. Based on the DNA35930 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO300.

Forward and reverse PCR primers were synthesized:

30 forward PCR primer 1 (35930_f1) 5'-GCCGCCTCATCTTCACGTTCTTCC-3' (SEQ ID NO:20)

forward PCR primer 2 (35930_f2) 5'-TCATCCAGCTGGTGCTGCTC-3' (SEQ ID NO:21)

forward PCR primer 3 (35930_f3) 5'-CTTCTTCCACTTCTGCCTGG-3' (SEQ ID NO:22)

forward PCR primer 4 (35930_f4) 5'-CCTGGGCAAAAATGCAAC-3' (SEQ ID NO:23)

reverse PCR primer 1 (35930_r1) 5'-CAGGAATGTAGAAGGCACCCACGG-3' (SEQ ID NO:24)

35 reverse PCR primer 2 (35930_r2) 5'-TGGCACAGATCTTCACCCACACGG-3' (SEQ ID NO:25)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA35930 sequence which had the following nucleotide sequence

hybridization probe (35930_p1)

5'-TGTCCATCATTATGCTGAGCCCAGGGCGTGGAGAGTCAGCTCTACAAGCTG-3' (SEQ ID NO:26)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO300 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO300
5 [herein designated as UNQ263 (DNA40625-1189)] (SEQ ID NO:18) and the derived protein sequence for PRO300.

The entire nucleotide sequence of UNQ263 (DNA40625-1189) is shown in Figure 8 (SEQ ID NO:18). Clone UNQ263 (DNA40625-1189) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 45-47 and ending at the stop codon at nucleotide positions 1416-1418 (Figure 8). The predicted polypeptide precursor is 457 amino acids long (Figure 9). Clone UNQ263 (DNA40625-1189) has been
10 deposited with ATCC and is assigned ATCC deposit no. 209788.

Analysis of the amino acid sequence of the full-length PRO300 polypeptide suggests that portions of it possess significant homology to the Diff 33 protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO300 amino acid sequence and the following Dayhoff sequence, HSU49188_1.
15

EXAMPLE 6: Isolation of cDNA Clones Encoding Human PRO284

Two cDNA sequences were isolated in the amylase screen described in Example 2 and those cDNA sequences are herein designated DNA12982 (see Figure 12; human placenta-derived) and DNA15886 (see Figure 13; human salivary gland-derived). The DNA12982 and DNA15886 sequences were then clustered and aligned,
20 giving rise to a consensus nucleotide sequence herein designated DNA18832.

Based on the DNA18832 consensus sequence, oligonucleotide probes were generated and used to screen a human placenta library (LIB89) prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

25 PCR primers (forward and reverse) were synthesized:

forward PCR primer 1 (18832.est.f) 5'-TCGTACAGTTACGCTCTCCC-3' (SEQ ID NO:31)

forward PCR primer 2 (18832.f) 5'-CTTGAGGAGCGTCAGAACGCG-3' (SEQ ID NO:32)

reverse PCR primer (18832.r) 5'-ATAACGAATGAAGCCTCGTG-3' (SEQ ID NO:33)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA18832 sequence which
30 had the following nucleotide sequence

hybridization probe (18832.p)

5'-GCTAATATCTGTAAGACGGCAGCTACAGCAGGCATCATGG-3' (SEQ ID NO:34)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones
35 encoding the PRO284 gene using the probe oligonucleotide and one of the PCR primers.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 167-169 and ending at the stop codon found at nucleotide positions 1022-1024 (Figure 10; SEQ ID NO:27). The predicted polypeptide precursor is 285 amino acids long, has a calculated molecular weight of approximately 32,190 daltons and an estimated pI of approximately 9.03. Analysis of the full-

length PRO284 sequence shown in Figure 11 (SEQ ID NO:28) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 24, transmembrane domains from about amino acid 76 to about amino acid 96 and from about amino acid 171 to about amino acid 195 and a potential N-glycosylation site from about amino acid 153 to about amino acid 156. Clone UNQ247 (DNA23318-1211) has been deposited with ATCC on April 21, 1998 and is assigned ATCC deposit no. 209787.

5 Analysis of the amino acid sequence of the full-length PRO284 polypeptide suggests that it possesses no significant sequence similarity to any known protein. However, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO284 amino acid sequence and the following Dayhoff sequences, JQ0124, CELE04A4_5, AB006451_1, AF030162_1, IM23_YEAST, S71194, NIA_CUCMA, IM17_YEAST, I50479 and HUMZFHP_1.

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EXAMPLE 7: Isolation of cDNA Clones Encoding Human PRO296

A cDNA sequence isolated in the amylase screen as described in Example 2 above was found, by BLAST and FastA sequence alignment, to have sequence homology to a nucleotide sequence encoding sarcoma-associated protein SAS. This cDNA sequence is herein designated DNA23020 (see Figure 16). The DNA23020 sequence was 15 then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., *Methods in Enzymology* 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA 20 sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington; <http://bozeman.mbt.washington.edu/phrap.docs/phrap.html>). The consensus sequence obtained therefrom is herein designated DNA35858. Two proprietary Genentech ESTs were employed in the assembly wherein those EST sequences are herein identified as DNA21971 (Figure 17; SEQ ID NO:38) and DNA29037 (Figure 18; SEQ ID NO:39).

25 Based on the DNA35858 consensus sequence, oligonucleotide probes were generated and used to screen a human kidney library (LIB228) library prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

PCR primers (forward and reverse) were synthesized:

30 forward PCR primer 1 (35858.f1) 5'-ACCCACGTCTGCGTTGCTGCC-3' (SEQ ID NO:40)

forward PCR primer 2 (35858.f2) 5'-GAGAACATATGCTGGAGAGG-3' (SEQ ID NO:41)

reverse PCR primer (35858.r1) 5'-AGGAATGCACTAGGATTGCGCGG-3' (SEQ ID NO:42)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA35858 sequence which had the following nucleotide sequence

35 hybridization probe (35858.p1)

5'-GGCCCCAAAGGCAAGGACAAAGCAGCTGTCAGGGAACCTCCGCCG-3' (SEQ ID NO:43)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO296 gene using the probe oligonucleotide and one of the PCR primers.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 174-176 and ending at the stop codon found at nucleotide positions 786-788 (Figure 14; SEQ ID NO:35). The predicted polypeptide precursor is 204 amino acids long, has a calculated molecular weight of approximately 22,147 daltons and an estimated pI of approximately 8.37. Analysis of the full-length PRO296 sequence shown in Figure 15 (SEQ ID NO:36) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 34 and transmembrane domains from about amino acid 47 to about amino acid 63, from about amino acid 72 to about amino acid 95 and from about amino acid 162 to about amino acid 182. Clone UNQ260 (DNA39979-1213) has been deposited with ATCC on April 21, 1998 and is assigned ATCC deposit no. 209789.

Analysis of the amino acid sequence of the full-length PRO296 polypeptide suggests that it possesses significant sequence similarity to the sarcoma-amplified SAS protein, thereby indicating that PRO296 may be a novel SAS homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO296 amino acid sequence and the following Dayhoff sequences, IS8391, GEN11061, SSC2B04_1, HSU81031_2, CD63_RAT, CD63_MOUSE, CD63_HUMAN, AF022813_1, CD63_RABIT and CO02_HUMAN.

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EXAMPLE 8: Isolation of cDNA Clones Encoding Human PRO329

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA35612. Based on the DNA35612 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO329.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 1 (35612_f1) 5'-TGGGCTGTGTCCTCATGG-3' (SEQ ID NO:46)

forward PCR primer 2 (35612_f2) 5'-TTTCCAGCGCCAATTCTC-3' (SEQ ID NO:47)

reverse PCR primer 1 (35612_r1) 5'-AGTTCTTGGACTGTGATAGCCAC-3' (SEQ ID NO:48)

25 reverse PCR primer 2 (35612_r2) 5'-AAACTTGGTTGTCCTCAGTGGCTG-3' (SEQ ID NO:49)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA35612 sequence which had the following nucleotide sequence

hybridization probe (35612_p1)

5'-GTGAGGGACCTGTCACTGAGGAGAGCAGCTGCCACACGGAGG-3' (SEQ ID NO:50)

30 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO329 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver tissue (LIB6).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO329 35 [herein designated as UNQ291 (DNA40594-1233)] (SEQ ID NO:44) and the derived protein sequence for PRO329.

The entire nucleotide sequence of UNQ291 (DNA40594-1233) is shown in Figure 19 (SEQ ID NO:44). Clone UNQ291 (DNA40594-1233) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 9-11 and ending at the stop codon at nucleotide positions 1086-1088 (Figure 19). The predicted polypeptide precursor is 359 amino acids long (Figure 20). The full-length PRO329 protein shown in

Figure 20 has an estimated molecular weight of about 38,899 daltons and a pI of about 5.21. Clone UNQ291 (DNA40594-1233) has been deposited with ATCC on February 5, 1998 and is assigned ATCC deposit no. 209617.

Analysis of the amino acid sequence of the full-length PRO329 polypeptide suggests that it possesses significant sequence similarity to a high affinity immunoglobulin F_c receptor protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO329 amino acid sequence and the following Dayhoff sequences, FCG1_HUMAN, FCG0_HUMAN, P_R91439, P_R22549, P_R91438, P_W00859, P_R20811, P_R22550, HUMCD6406_1 and FCG1_MOUSE.

EXAMPLE 9: Isolation of cDNA Clones Encoding Human PRO362

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, 10 wherein the consensus sequence obtained is herein designated DNA42257. Based on the DNA42257 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO362.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 1 (42257.f1) 5'-TATCCCTCCAATTGAGCACCCTGG-3' (SEQ ID NO:53)

15 forward PCR primer 2 (42257.f2) 5'-GTCGGAAGACATCCAAACAAG-3' (SEQ ID NO:54)

reverse PCR primer 1 (42257.r1) 5'-CTTCACAATGTCGCTGTGCTGCTC-3' (SEQ ID NO:55)

reverse PCR primer 2 (42257.r2) 5'-AGCCAAATCCAGCAGCTGGCTTAC-3' (SEQ ID NO:56)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA42257 sequence which had the following nucleotide sequence

20 hybridization probe (42257.p1)

5'-TGGATGACCGGAGCCACTACACGTGTGAAGTCACCTGGCAGACTCCTGAT-3' (SEQ ID NO:57)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO362 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of 25 the cDNA libraries was isolated from human fetal brain tissue (LIB153).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO362 [herein designated as UNQ317 (DNA45416-1251)] (SEQ ID NO:51) and the derived protein sequence for PRO362.

The entire nucleotide sequence of UNQ317 (DNA45416-1251) is shown in Figure 21 (SEQ ID NO:51). Clone UNQ317 (DNA45416-1251) contains a single open reading frame with an apparent translational initiation site 30 at nucleotide positions 119-121 and ending at the stop codon at nucleotide positions 1082-1084 (Figure 21). The predicted polypeptide precursor is 321 amino acids long (Figure 22). The full-length PRO362 protein shown in Figure 2 has an estimated molecular weight of about 35,544 daltons and a pI of about 8.51. Analysis of the full-length PRO362 polypeptide as shown in Figure 22 evidences the presence of a glycosaminoglycan attachment site at about 35 amino acid 149 to about amino acid 152 and a transmembrane domain from about amino acid 276 to about amino acid 306. Clone UNQ317 (DNA45416-1251) has been deposited with ATCC on February 5, 1998 and is assigned ATCC deposit no. 209620.

Analysis of the amino acid sequence of the full-length PRO362 polypeptide suggests that it possesses significant sequence similarity to the A33 antigen protein and the HCAR protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO362 amino acid

sequence and the following Dayhoff sequences, AB002341_1, HSU55258_1, HSC7NRCAM_1, RNU81037_1, A33_HUMAN, P_W14158, NMNCAMRI_1, HSTITINN2_1, S71824_1 and HSU63041_1.

EXAMPLE 10: Isolation of cDNA Clones Encoding Human PRO363

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above,
5 wherein the consensus sequence obtained is herein designated DNA42828. Based on the DNA42828 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO363.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer (42828.f1) 5'-CCAGTGCACAGCAGGCAACGAAGC-3' (SEQ ID NO:60)

10 reverse PCR primer (42828.r1) 5'-ACTAGGCTGTATGCCTGGGTGGGC-3' (SEQ ID NO:61)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA42828 sequence which had the following nucleotide sequence

hybridization probe (42828.p1)

5'-GTATGTACAAAGCATCGGCATGGTTCAGGAGCAGTGACAGGC-3' (SEQ ID NO:62)

15 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO363 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

20 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO363 [herein designated as UNQ318 (DNA45419-1252)] (SEQ ID NO:58) and the derived protein sequence for PRO363.

The entire nucleotide sequence of UNQ318 (DNA45419-1252) is shown in Figure 23 (SEQ ID NO:58). Clone UNQ318 (DNA45419-1252) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 190-192 and ending at the stop codon at nucleotide positions 1309-1311 (Figure 23). The predicted polypeptide precursor is 373 amino acids long (Figure 24). The full-length PRO363 protein shown in
25 Figure 24 has an estimated molecular weight of about 41,281 daltons and a pI of about 8.33. A transmembrane domain exists at amino acids 221 to 254 of the amino acid sequence shown in Figure 24 (SEQ ID NO:59). The PRO363 polypeptide also possesses at least two myelin P0 protein domains from about amino acids 15 to 56 and from about amino acids 87 to 116. Clone UNQ318 (DNA45419-1252) has been deposited with ATCC on February 5, 1998 and is assigned ATCC deposit no. 209616.

30 Analysis of the amino acid sequence of the full-length PRO363 polypeptide suggests that it possesses significant sequence similarity to the cell surface protein HCAR, thereby indicating that PRO363 may be a novel HCAR homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO363 amino acid sequence and the following Dayhoff sequences, HS46KDA_1, HSU90716_1, MMCARH_1, MMCARHOM_1, MMU90715_1, A33_HUMAN, P_W14146, P_W14158, A42632
35 and B42632.

EXAMPLE 11: Isolation of cDNA Clones Encoding Human PRO868

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA38133. Based on the DNA38133 consensus

sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO868.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer (38133.f1) 5'-GTAGCAGTGCACATGGGGTGTG-3' (SEQ ID NO:65)

reverse PCR primer (38133.r1) 5'-ACCGCACATCCTCAGTCTCTGTCC-3' (SEQ ID NO:66)

- 5 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA38133 sequence which had the following nucleotide sequence

hybridization probe (38133.p1)

5'-ACGATGATCGCGGGCTCCCTCTCCTGCTGGATTCTTAGCACCACCAC-3' (SEQ ID NO:67)

- In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened
10 by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO868 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO868 [herein designated as UNQ437 (DNA52594-1270)] (SEQ ID NO:63) and the derived protein sequence for PRO868.

- 15 The entire nucleotide sequence of UNQ437 (DNA52594-1270) is shown in Figure 25 (SEQ ID NO:63). Clone UNQ437 (DNA52594-1270) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 325-327 and ending at the stop codon at nucleotide positions 2290-2292 (Figure 25). The predicted polypeptide precursor is 655 amino acids long (Figure 26). The full-length PRO868 protein shown in Figure 26 has an estimated molecular weight of about 71,845 daltons and a pI of about 8.22. Analysis of the full-
20 length PRO868 polypeptide sequence demonstrates the presence of conserved cysteine-containing domains from about amino acid 66 to about amino acid 78 and from about amino acid 123 to about amino acid 134 of the sequence shown in Figure 26 (SEQ ID NO:3), a TNFR death domain from about amino acid 85 to about amino acid 110, a FASA_mouse death domain block from about amino acid 159 to about amino acid 175 and a transmembrane domain from about amino acid 347 to about amino acid 375. Clone UNQ437 (DNA52594-1270) has been deposited with
25 ATCC on March 17, 1998 and is assigned ATCC deposit no. 209679

- Analysis of the amino acid sequence of the full-length PRO868 polypeptide suggests that it possesses significant sequence similarity to the tumor necrosis factor receptor protein, thereby indicating that PRO868 may be a novel member of the tumor necrosis factor receptor family. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO868 amino acid sequence and the
30 following Dayhoff sequences, RNU94330_1, P_R99933, P_R99945, P_R99950, HSU94332_1, CD40_HUMAN, S63368_1, TNR2_HUMAN, MVU87844_1 AND CVU87837_1.

EXAMPLE 12: Isolation of cDNA Clones Encoding Human PRO382

- A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above,
35 wherein the consensus sequence obtained is herein designated DNA30892. Based on the DNA30892 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO382.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-TGACATGCCCTTATGAAGCTGGC-3' (SEQ ID NO:70)

reverse PCR primer 5'-TACACGTCCCTGTGGTTGCAGATC-3' (SEQ ID NO:71)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA30892 sequence which had the following nucleotide sequence

hybridization probe

5'-CGTTCAATGCAGAAATGATCCAGCCTGTGCCTGCCAACTCTGAAGAG-3' (SEQ ID NO:72)

5 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO382 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

10 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO382 [herein designated as UNQ323 (DNA45234-1277)] (SEQ ID NO:68) and the derived protein sequence for PRO382.

The entire nucleotide sequence of UNQ323 (DNA45234-1277) is shown in Figure 27 (SEQ ID NO:68). Clone UNQ323 (DNA45234-1277) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 126-128 and ending at the stop codon at nucleotide positions 1485-1487 (Figure 27). The predicted polypeptide precursor is 453 amino acids long (Figure 28). The full-length PRO382 protein shown in 15 Figure 28 has an estimated molecular weight of about 49,334 daltons and a pI of about 6.32. Analysis of the native PRO382 amino acid sequence shown in Figure 28 (SEQ ID NO:69) indicates the presence of a putative transmembrane domain from about amino acid 240 to about amino acid 284, a putative signal peptide at about amino acid 1 to about amino acid 20, a putative apple domain at about amino acid 386 to about amino acid 419, a putative Kringle domain at about amino acid 394 to about amino acid 406 and a histidine-containing protease active site at 20 about amino acid 253 to about amino acid 258. Clone UNQ323 (DNA45234-1277) has been deposited with ATCC on March 5, 1998 and is assigned ATCC deposit no. 209654.

Analysis of the amino acid sequence of the full-length PRO382 polypeptide suggests that it possess significant homology to serine protease proteins, thereby indicating that PRO382 may be a novel serine protease. Specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology 25 between the PRO382 amino acid sequence and the following Dayhoff sequences, HSU75329_1, ENTK_MOUSE, HEPS_HUMAN, AF030065_1, HEPS_RAT, PLMN_PIG, P_R89430, P_R89435, PLMN_HORSE, PLMN_BOVIN and P_R83959.

EXAMPLE 13: Isolation of cDNA Clones Encoding Human PRO545

30 A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA44706. An EST proprietary to Genentech was employed in the consensus assembly and is herein designated DNA13217 (Figure 31; SEQ ID NO:75). Based on the DNA44706 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for 35 PRO545.

Forward and reverse PCR primers were synthesized:

forward PCR primer 1 5'-GTCTCAGCACGTGTTCTGGTCTCAGGG-3' (SEQ ID NO:76)

forward PCR primer 2 5'-CATGAGCATGTGCACGGC-3' (SEQ ID NO:77)

forward PCR primer 3 5'-TACCTGCACGATGGGCAC-3' (SEQ ID NO:78)

forward PCR primer 4 5'-CACTGGGCACCTCCCTTC-3' (SEQ ID NO:79)

reverse PCR primer 1 5'-CTCCAGGCTGGTCTCCAAGTCCTTC-3' (SEQ ID NO:80)

reverse PCR primer 2 5'-TCCCTGTTGGACTCTGCAGCTTCC-3' (SEQ ID NO:81)

reverse PCR primer 3 5'-CTTCGCTGGGAAGAGTTG-3' (SEQ ID NO:82)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA44706

5 sequence which had the following nucleotide sequence

hybridization probe

5'-GTGCAACCAACAGATACAAACTTCCCAGCGAAGAAGCTGAAAAGCGTC-3'

(SEQ ID NO:83)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened
10 by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO545 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human placenta tissue (LIB90).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO545 [herein designated as UNQ346 (DNA49624-1279)] (SEQ ID NO:73) and the derived protein sequence for PRO545.

15 The entire nucleotide sequence of UNQ346 (DNA49624-1279) is shown in Figure 29 (SEQ ID NO:73). Clone UNQ346 (DNA49624-1279) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 311-313 and ending at the stop codon at nucleotide positions 2516-2518 (Figure 29). The predicted polypeptide precursor is 735 amino acids long (Figure 30). The full-length PRO545 protein shown in Figure 30 has an estimated molecular weight of about 80,177 daltons and a pI of about 7.08. Important regions of 20 the PRO545 amino acid sequence include the signal peptide, corresponding to amino acids 1-28, five potential N-glycosylation sites, from about amino acid 111-114, amino acids 146-149, amino acids 348-351, amino acids 449-452, and amino acids 648-651, and a neutral zinc metallopeptidase, zinc-binding region signature sequence, from about amino acids 344-353. Clone UNQ346 (DNA49624-1279) has been deposited with ATCC and is assigned ATCC deposit no. 209655.

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EXAMPLE 14: Isolation of cDNA Clones Encoding Human PRO617

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA42798. Based on the DNA42798 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 30 2) for use as probes to isolate a clone of the full-length coding sequence for PRO617.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-ACGGGCACACTGGATCCCAAATG-3' (SEQ ID NO:86)

reverse PCR primer 5'-GGTAGAGATGTAGAAGGGCAAGCAAGACC-3' (SEQ ID NO:87)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA42798

35 sequence which had the following nucleotide sequence

hybridization probe

5'-GCTCCCTACCCGTGCAGGTTCTTCATTGTTCTTAACCAGTATGCCG-3' (SEQ ID NO:88)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones

encoding the PRO617 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO617 [herein designated as UNQ353 (DNA48309-1280)] (SEQ ID NO:1) and the derived protein sequence for PRO617.

The entire nucleotide sequence of UNQ353 (DNA48309-1280) is shown in Figure 32 (SEQ ID NO:84).

- 5 Clone UNQ353 (DNA48309-1280) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 723-725 and ending at the stop codon at nucleotide positions 924-926 (Figure 32). The predicted polypeptide precursor is 67 amino acids long (Figure 33). The full-length PRO617 protein shown in Figure 10 33 has an estimated molecular weight of about 6,981 daltons and a pI of about 7.47. Analysis of the PRO617 amino acid sequence also evidences the existence of a putative signal peptide from about amino acid 15 to about amino acid 27 and a putative protein kinase C phosphorylation site from about amino acid 41 to about amino acid 43. Clone 15 UNQ353 (DNA48309-1280) has been deposited on March 5, 1998 with ATCC and is assigned ATCC deposit no. 209656.

Analysis of the amino acid sequence of the full-length PRO617 polypeptide suggests that it possesses significant homology to the CD24 protein, thereby indicating that PRO617 may be a novel CD24 homolog. More 15 specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO617 amino acid sequence and the following Dayhoff sequences, CD24_HUMAN, CD24_MOUSE, S15785, CD24_RAT, VGE_BPG4, MSE5_HUMAN, HSMHC3W36A_2, MLU15184_8, P R85075, SEPL_HUMAN and MTCY63_13.

20 **EXAMPLE 15: Isolation of cDNA Clones Encoding Human PRO700**

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA30837. Based on the DNA30837 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO700.

25 Forward and reverse PCR primers were synthesized:

forward PCR primer 1 5'-ATGTTCTCGCGCCCTGGTG-3' (SEQ ID NO:91)

forward PCR primer 2 5'-CCAAGCCAACACACTCTACAG-3' (SEQ ID NO:92)

reverse PCR primer 1 5'-AAGTGGTCGCCTTGTGCAACGTGC-3' (SEQ ID NO:93)

reverse PCR primer 2 5'-GGTCAAAGGGATATATGCCAC-3' (SEQ ID NO:94)

30 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA30837 sequence which had the following nucleotide sequence

hybridization probe

5'-GCATGGAAGATGCCAAAGTCTATGTGGCTAAAGTGGACTGCACGGCCCA-3'

(SEQ ID NO:95)

35 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO700 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO700 [herein designated as UNQ364 (DNA46776-1284)] (SEQ ID NO:89) and the derived protein sequence for PRO700.

The entire nucleotide sequence of UNQ364 (DNA46776-1284) is shown in Figure 34 (SEQ ID NO:89). Clone UNQ364 (DNA46776-1284) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 33-35 and ending at the stop codon at nucleotide positions 1329-1331 (Figure 34). The 5 predicted polypeptide precursor is 432 amino acids long (Figure 35). The full-length PRO700 protein shown in Figure 35 has an estimated molecular weight of about 47,629 daltons and a pI of about 5.90. Important regions of the amino acid sequence of PRO700 include the signal peptide, corresponding to amino acids from about 1 to 33, regions homologous to disulfide isomerase, corresponding to amino acids from about 82-99, 210-255, and 345-360, a tyrosine kinase phosphorylation site, corresponding to amino acids from about 143-151, and an endoplasmic 10 reticulum targeting sequence, corresponding to amino acids from about 429-432. Clone UNQ364 (DNA46776-1284) has been deposited with ATCC and is assigned ATCC Deposit No. 209721.

EXAMPLE 16: Isolation of cDNA Clones Encoding Human PRO702

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, 15 wherein the consensus sequence obtained is herein designated DNA36623. Based on the DNA36623 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO702.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer (36623.f1) 5'-CGCTGACTATGTTGCCAAGAGTGG-3' (SEQ ID NO:98)

20 reverse PCR primer (36623.r1) 5'-GATGATGGAGGCTCCATACCTCAG-3' (SEQ ID NO:99)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA36623 sequence which had the following nucleotide sequence

hybridization probe (36623.p1)

5'-GTGTTCATGGCGTGAATGACCTTGAAAGGGAGGGACAGTACATGTCAC-3' (SEQ ID NO:100)

25 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO702 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver tissue (LIB229).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO702 30 [herein designated as UNQ366 (DNA50980-1286)] (SEQ ID NO:96) and the derived protein sequence for PRO702.

The entire nucleotide sequence of UNQ366 (DNA50980-1286) is shown in Figure 36 (SEQ ID NO:96). Clone UNQ366 (DNA50980-1286) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 22-24 and ending at the stop codon at nucleotide positions 853-855 (Figure 36). The predicted polypeptide precursor is 277 amino acids long (Figure 37). The full-length PRO702 protein shown in Figure 37 has 35 an estimated molecular weight of about 30,645 daltons and a pI of about 7.47. Analysis of the full-length native PRO702 amino acid sequence evidences the presence of a putative signal peptide from about amino acid 1 to about amino acid 25, potential N-glycosylation sites from about amino acid 230 to about amino acid 233 and from about amino acid 258 to about amino acid 261 and a C-type lectin domain signature sequence from about amino acid 248 to about amino acid 270. Clone UNQ366 (DNA50980-1286) has been deposited with ATCC on March 31, 1998 and

is assigned ATCC deposit no. 209717.

Analysis of the amino acid sequence of the full-length PRO702 polypeptide suggests that it possesses significant sequence similarity to the conglutinin protein, thereby indicating that PRO702 may be a novel conglutinin homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO702 amino acid sequence and the following Dayhoff sequences, S32436, P_R75642, P_W18780, P_W18781, A53330, AC002528_1, HSPPA2IC0_1, CA21_HUMAN, CA14_HUMAN and A61262.

EXAMPLE 17: Isolation of cDNA Clones Encoding Human PRO703

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA43047. Based on the DNA43047 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO703.

Forward and reverse PCR primers were synthesized:

forward PCR primer 5'-GAGAGCCATGGGGCTCCACCTG-3' (SEQ ID NO:103)

reverse PCR primer 1 5'-GGAGAATGTGGCCACAAC-3' (SEQ ID NO:104)

15 reverse PCR primer 2 5'-GCCCTGGCACAGTGACTCCATAGACG-3' (SEQ ID NO:105)

reverse PCR primer 3 5'-ATCCACTTCAGCGGACAC-3' (SEQ ID NO:106)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40654 sequence which had the following nucleotide sequence

hybridization probe

20 5'-CCAGTGCAGGATACCTCTTCCCCCAGAGCATAACAGACACG-3'

(SEQ ID NO:107)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO703 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO703 [herein designated as UNQ367 (DNAS0913-1287)] (SEQ ID NO:101) and the derived protein sequence for PRO703.

The entire nucleotide sequence of UNQ367 (DNAS0913-1287) is shown in Figure 38 (SEQ ID NO:101). Clone UNQ367 (DNAS0913-1287) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 115-117 and ending at the stop codon at nucleotide positions 2305-2307 (Figure 38). The predicted polypeptide precursor is 730 amino acids long (Figure 39). The full-length PRO703 protein shown in Figure 39 has an estimated molecular weight of about 78,644 daltons, and a pI of about: 7.65. Important regions of the PRO703 amino acid sequence include the signal peptide, a cAMP- and cGMP-dependent protein kinase phosphorylation site, a CUB domain protein motif, N-glycosylation sites and a putative AMP-binding domain signature. Clone UNQ367 (DNAS0913-1287) has been deposited with ATCC and is assigned ATCC deposit no. 209716.

EXAMPLE 18: Isolation of cDNA Clones Encoding Human PRO705

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA43437. Based on the DNA43437 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO705.

5 A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-AAGCGTGACAGCGGGCACGTC-3' (SEQ ID NO:110)

reverse PCR primer 5'-TGCACAGTCTCTGCAGTGCCCAGG-3' (SEQ ID NO:111)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA43437 sequence which had the following nucleotide sequence

10 hybridization probe (43437.p1)

5'-GAATGCTGGAACGGGCACAGCAAAGCCAGATACTTGCCTG-3' (SEQ ID NO:112)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO705 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of 15 the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO705 [herein designated as UNQ369 (DNA50914-1289)] (SEQ ID NO:108) and the derived protein sequence for PRO705.

The entire nucleotide sequence of UNQ369 (DNA50914-1289) is shown in Figure 40 (SEQ ID NO:108). Clone UNQ369 (DNA50914-1289) contains a single open reading frame with an apparent translational initiation site 20 at nucleotide positions 566-568 and ending at the stop codon at nucleotide positions 2231-2233 (Figure 40). The predicted polypeptide precursor is 555 amino acids long (Figure 41). The full-length PRO705 protein shown in Figure 41 has an estimated molecular weight of about 62,736 daltons and a pI of about 5.36. Analysis of the full-length PRO705 sequence as shown in Figure 41 evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 23, a eukaryotic DNA topoisomerase I active site from about amino acid 418 to 25 about amino acid 436, and various regions that show homology to various glypcan proteins from about amino acid 237 to about amino acid 279, about amino acid 421 to about amino acid 458, about amino acid 53 to about amino acid 74, about amino acid 466 to about amino acid 504, about amino acid 308 to about amino acid 355, about amino acid 104 to about amino acid 156 and about amino acid 379 to about amino acid 410. Clone UNQ369 (DNA50914-1289) has been deposited with ATCC on March 31, 1998 and is assigned ATCC deposit no.209722.

30 Analysis of the amino acid sequence of the full-length PRO705 polypeptide suggests that it possesses significant sequence similarity to the K-glycan protein, thereby indicating that PRO705 may be a novel glycan protein family member. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO705 amino acid sequence and the following Dayhoff sequences, GPC1_MOUSE, GLYP_CHICK, GLYP_RAT, GLYP_HUMAN, GPC2_RAT, GPC5_HUMAN, GPC3_HUMAN, 35 GPC3_RAT, P_R30168 and CEC03H12_2.

EXAMPLE 19: Isolation of cDNA Clones Encoding Human PRO708

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA34024. Based on the DNA34024 consensus

sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO708.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CCCAACCCAACCTGTTACCTCTGG-3' (SEQ ID NO:115)

reverse PCR primer 5'-CTCTCTGAGTGTACATCTGTGTGG-3' (SEQ ID NO:116)

- 5 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA34024 sequence which had the following nucleotide sequence

hybridization probe

5'-GCCACCCTACCTCAGAAACTGAAGGAGGTTGGNTATTCAACGCATATGGTCGG-3' (SEQ ID NO:117)

- In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened
10 by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO708 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human bone marrow tissue (LIB255).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO708 [herein designated as UNQ372 (DNA48296-1292)] (SEQ ID NO:113) and the derived protein sequence for PRO708.

- 15 The entire nucleotide sequence of UNQ372 (DNA48296-1292) is shown in Figures 42A-B (SEQ ID NO:113). Clone UNQ372 (DNA48296-1292) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 891-893 and ending at the stop codon at nucleotide positions 2436-2438 (Figures 42A-B). The predicted polypeptide precursor is 515 amino acids long (Figure 43). The full-length PRO708 protein shown in Figure 43 has an estimated molecular weight of about 56,885 daltons and a pI of about 6.49. Analysis of
20 the PRO708 amino acid sequence shown in Figure 43 (SEQ ID NO:114) evidences the existence of a putative signal peptide at about amino acid 1 to about amino acid 37, putative sulfatase signature sequences at about amino acid 120 to about amino acid 132 and about amino acid 168 to about amino acid 177, a putative tyrosine kinase phosphorylation site from about amino acid 163 to about amino acid 169 and potential N-glycosylation sites from about amino acid 157 to about amino acid 160, about amino acid 306 to about amino acid 309 and about amino acid 318 to about amino
25 acid 321. Clone UNQ372 (DNA48296-1292) has been deposited with ATCC on March 11, 1998 and is assigned ATCC deposit no. 209668.

Analysis of the amino acid sequence of the full-length PRO708 polypeptide suggests that it possesses significant homology to the aryl sulfatase proteins, thereby indicating that PRO708 may be a novel aryl sulfatase homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant
30 homology between the PRO708 amino acid sequence and the following Dayhoff sequences, ARSB_HUMAN, CELCS4D2_2, G02857, STS_HUMAN, I37186, I37187, GEN12648, CELD1014_7, GA6S_HUMAN and SPHM_HUMAN.

EXAMPLE 20: Isolation of cDNA Clones Encoding Human PRO320

- 35 A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA28739. Based on the DNA28739 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO320.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CCTCAGTGGCCACATGCTCATG-3' (SEQ ID NO:120)

reverse PCR primer 5'-GGCTGCACGTATGGCTATCCATAG-3' (SEQ ID NO:121)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA28739 sequence which had the following nucleotide sequence

5 hybridization probe

5'-GATAAACTGTCAGTACAGCTGTGAAGACACAGAAGAAGGGCACAGTGCC-3' (SEQ ID NO:122)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO320 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of 10 the cDNA libraries was isolated from human fetal lung tissue (LIB25).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO320 [herein designated as UNQ281 (DNA32284-1307)] (SEQ ID NO:118) and the derived protein sequence for PRO320.

The entire nucleotide sequence of UNQ281 (DNA32284-1307) is shown in Figure 44 (SEQ ID NO:118).

Clone UNQ281 (DNA32284-1307) contains a single open reading frame with an apparent translational initiation site 15 at nucleotide positions 135-137 and ending at the stop codon at nucleotide positions 1149-1151 (Figure 44). The predicted polypeptide precursor is 338 amino acids long (Figure 45). The full-length PRO320 protein shown in Figure 45 has an estimated molecular weight of about 37,143 daltons and a pI of about 8.92. Important regions of the PRO320 amino acid sequence include the signal peptide, corresponding to amino acids 1-21, an EGF-like domain cysteine pattern signature, corresponding to amino acids 80-91, and three calcium-binding EGF-like domains, 20 corresponding to amino acids 103-124, 230-151 and 185-206, respectively. Clone UNQ281 (DNA32284-1307) has been deposited with ATCC and is assigned ATCC deposit no. 209670.

EXAMPLE 21: Isolation of cDNA Clones Encoding Human PRO324

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, 25 wherein the consensus sequence obtained is herein designated DNA34347. Based on the DNA34347 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO324.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 1 5'-GCAATGAACCTGGGAGCTGC-3' (SEQ ID NO:125)

30 forward PCR primer 2 5'-CTGTGAATAGCATCCTGGG-3' (SEQ ID NO:126)

forward PCR primer 3 5'-CTTTCAAGCCACTGGAGGG-3' (SEQ ID NO:127)

reverse PCR primer 1 5'-CTGTAGACATCCAAGCTGGTATCC-3' (SEQ ID NO:128)

reverse PCR primer 2 5'-AAGAGTCTGCATCCACACCACTC-3' (SEQ ID NO:129)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA34347 35 sequence which had the following nucleotide sequence

hybridization probe

5'-ACCTGACGCTACTATGGGCCGAGTGGCAGGGACGACGCCAGAATG-3' (SEQ ID NO:130)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate

clones encoding the PRO324 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver tissue (LIB6).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO324 [herein designated as UNQ285 (DNA36343-1310)] (SEQ ID NO:123) and the derived protein sequence for PRO324.

The entire nucleotide sequence of UNQ285 (DNA36343-1310) is shown in Figure 46 (SEQ ID NO:123).

- 5 Clone UNQ285 (DNA36343-1310) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 144-146 and ending at the stop codon at nucleotide positions 1011-1013 (Figure 46). The predicted polypeptide precursor is 289 amino acids long (Figure 47). The full-length PRO324 protein shown in Figure 47 has an estimated molecular weight of about 32,268 daltons and a pI of about 9.21. Analysis of the PRO324 polypeptide sequence shown in Figure 47 (SEQ ID NO:124) evidence the presence of the following: a signal peptide
- 10 from about amino acid 1 to about amino acid 31, a transmembrane domain from about amino acid 136 to about amino acid 157, tyrosine kinase phosphorylation sites from about amino acid 106 or about amino acid 107 to about amino acid 113 and regions that are homologous to short-chain alcohol dehydrogenase regions from about amino acid 80 to about amino acid 90, from about amino acid 131 to about amino acid 168, from about amino acid 1 to about amino acid 13 and from about amino acid 176 to about amino acid 185. Clone UNQ285 (DNA36343-1310) has been
- 15 deposited with ATCC on March 30, 1998 and is assigned ATCC deposit no. 209718.

- Analysis of the amino acid sequence of the full-length PRO324 polypeptide suggests that it possesses significant sequence similarity to oxidoreductases, thereby indicating that PRO324 may be a novel oxidoreductase homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO324 amino acid sequence and the following Dayhoff sequences, B61209, A69965,
- 20 YQJQ_BACSU, D69930, S76124, FABG_ECOLI, C70023, S77280, FABG_VIBHA and MTV013_6.

EXAMPLE 22: Isolation of cDNA Clones Encoding Human PRO351

- A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA35950. Based on the DNA35950 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO351.

Forward and reverse PCR primers were synthesized:

forward PCR primer 5'-CCTGTGCTGTGCCTCGAGCCTGAC-3' (SEQ ID NO:133)

reverse PCR primer 5'-GTGGGCAGCAGTTAGCACCGCCTC-3' (SEQ ID NO:134)

- 30 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA35950 sequence which had the following nucleotide sequence

hybridization probe

5'-GGCTGGCATCATCAGTTGCATCAAGCTGTGCCAGGAGGACGC-3'

(SEQ ID NO:135)

- 35 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO351 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver tissue (LIB230).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO351 [herein designated as UNQ308 (DNA40571-1315)] (SEQ ID NO:131) and the derived protein sequence for PRO351.

The entire nucleotide sequence of UNQ308 (DNA40571-1315) is shown in Figure 48 (SEQ ID NO:131). Clone UNQ308 (DNA40571-1315) contains two open reading frames with an apparent translational initiation site at nucleotide positions 189-191 and a second open reading frame beginning at nucleotide 470, with the two open reading 5 frames ending at the stop codons at nucleotide positions 363-365 and 2009-2011, respectively (Figure 48). The predicted polypeptide precursor is 571 amino acids long (Figure 49). Important regions of the amino acid sequence of PRO351 include the signal peptide, regions having sequence similarity to serine proteases of the trypsin family, two N-glycosylation sites, and three Kringle domains. Clone UNQ308 (DNA40571-1315) has been deposited with ATCC and is assigned ATCC deposit no. 209784.

10

EXAMPLE 23: Isolation of cDNA Clones Encoding Human PRO352

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA36950. Based on the DNA36950 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of 15 interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO352.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 1 5'-CTGGCACAGCTAACCTCATCTGG-3' (SEQ ID NO:138)

forward PCR primer 2 5'-GCTGTCTGTCTGTCTCATTG-3' (SEQ ID NO:139)

forward PCR primer 3 5'-GGACACAGTATACTGACCAC-3' (SEQ ID NO:140)

20

reverse PCR primer 1 5'-TGCAGAACCAAGGCAGCTGTAAGTGC-3' (SEQ ID NO:141)

reverse PCR primer 2 5'-TGGAAAGAAGAGGGTGGTGATGTGG-3' (SEQ ID NO:142)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA36950 sequence which had the following nucleotide sequence

hybridization probe

25

5'-CAGCTGACAGACACCAAACAGCTGGTCACAGTTCACCGAAGGC-3' (SEQ ID NO:143)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO352 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

30

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO352 [herein designated as UNQ309 (DNA41386-1316)] (SEQ ID NO:136) and the derived protein sequence for PRO352.

The entire nucleotide sequence of UNQ309 (DNA41386-1316) is shown in Figure 50 (SEQ ID NO:136). Clone UNQ309 (DNA41386-1316) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 152-154 and ending at the stop codon at nucleotide positions 1100-1102 (Figure 50). The 35 predicted polypeptide precursor is 316 amino acids long (Figure 51). The full-length PRO352 protein shown in Figure 2 has an estimated pI of about 4.62. Analysis of the full-length PRO352 sequence evidences the presence of a signal peptide from about amino acid 1 to about amino acid 28, a transmembrane domain from about amino acid 251 to about amino acid 270, potential N-glycosylation sites from about amino acid 91 to about amino acid 94, about amino acid 104 to about amino acid 107, about amino acid 189 to about amino acid 192 and about amino acid 215

to about amino acid 218 and a region having homology to immunoglobulins and MHC from about amino acid 217 to about amino acid 234. Clone UNQ309 (DNA41386-1316) has been deposited with ATCC on March 26, 1998 and is assigned ATCC deposit no. 209703.

Analysis of the amino acid sequence of the full-length PRO352 polypeptide suggests that it possesses significant sequence similarity to the butyrophilin protein, thereby indicating that PRO352 is a novel butyrophilin homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO352 amino acid sequence and the following Dayhoff sequences, BUTY_HUMAN, HSB73_1, GGCD80_1, I46690, A33_HUMAN, P_R67988, CD86_MOUSE, P_R71360, B39371 and D50558_1.

EXAMPLE 24: Isolation of cDNA Clones Encoding Human PRO381

10 A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA39651. Based on the DNA39651 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO381.

15 A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CTTCCTTGCTTCAGCAACATGAGGC-3' (SEQ ID NO:146)
reverse PCR primer 5'-GCCAGAGCAGGAGGAATGATGAGC-3' (SEQ ID NO:147)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA39651 sequence which had the following nucleotide sequence

hybridization probe

20 5'-GTGGAACCGGGTCTTGACTCTGTCGTCATTCTTGATTGGGGCTTG-3' (SEQ ID NO:148)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO381 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

25 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO381 [herein designated as UNQ322 (DNA44194-1317)] (SEQ ID NO:144) and the derived protein sequence for PRO381.

The entire nucleotide sequence of UNQ322 (DNA44194-1317) is shown in Figure 52 (SEQ ID NO:144). Clone UNQ322 (DNA44194-1317) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 174-176 and ending at the stop codon at nucleotide positions 807-809 (Figure 52). The predicted polypeptide precursor is 211 amino acids long (Figure 53). The full-length PRO381 protein shown in Figure 53 has an estimated molecular weight of about 24,172 daltons and a pI of about 5.99. Analysis of the full-length PRO381 polypeptide shown in Figure 53 (SEQ ID NO:145) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 20, a potential N-glycosylation site from about amino acid 176 to about amino acid 179, potential casein kinase II phosphorylation sites from about amino acid 143 to about amino acid 146, from about amino acid 156 to about amino acid 159, from about amino acid 178 to about amino acid 181, and from about amino acid 200 to about amino acid 203, an endoplasmic reticulum targeting sequence from about amino acid 208 to about amino acid 211, FKBP-type peptidyl-prolyl cis-trans isomerase sites from about amino acid 78 to about amino acid 114 and from about amino acid 118 to about amino acid 131, EF-hand calcium binding sites from about amino acid 191 to about amino acid 203, from about amino acid 184 to about amino acid 203

and from about amino acid 140 to about amino acid 159, and an S-100/ICaBP type calcium binding domain from about amino acid 183 to about amino acid 203. Clone UNQ322 (DNA44194-1317) has been deposited with ATCC on April 28, 1998 and is assigned ATCC deposit no. 209808.

Analysis of the amino acid sequence of the full-length PRO381 polypeptide suggests that it possesses significant sequence similarity to FKBP immunophilin proteins, thereby indicating that PRO381 may be a novel FKBP immunophilin homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO381 amino acid sequence and the following Dayhoff sequences, AF040252_1, I49669, P_R93551, S71238, CELC05C8_1, CEU27353_1, MIP_TRYCR, CEZC455_3, FKB4_HUMAN and I40718.

10 **EXAMPLE 25: Isolation of cDNA Clones Encoding Human PRO386**

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA40674. Two proprietary Genentech EST sequences were employed in the consensus sequence assembly, wherein those EST sequences are herein designated DNA23350 (Figure 56; SEQ ID NO:151) and DNA23536 (Figure 57; SEQ ID NO:152). Based on the DNA40674 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO386.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-ACGGAGCATGGAGGTCCACAGTAC-3' (SEQ ID NO:153)

reverse PCR primer 5'-GCACGTTTCTCAGCATACCGAC-3' (SEQ ID NO:154)

20 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40674 sequence which had the following nucleotide sequence

hybridization probe

5'-CGCCTGCCCTGCACCTCAACTCCTGCTACACAGTGAACCACAAACAGTT-3' (SEQ ID NO:155)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened 25 by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO386 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal brain tissue (LIB153).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO386 [herein designated as UNQ326 (DNA45415-1318)] (SEQ ID NO:149) and the derived protein sequence for PRO386.

30 The entire nucleotide sequence of UNQ326 (DNA45415-1318) is shown in Figure 54 (SEQ ID NO:149). Clone UNQ326 (DNA45415-1318) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 146-148 and ending at the stop codon at nucleotide positions 791-793 (Figure 54). The predicted polypeptide precursor is 215 amino acids long (Figure 55). The full-length PRO386 protein shown in Figure 55 has an estimated molecular weight of about 24,326 daltons and a pI of about 6.32. Analysis of the full-length PRO386 sequence shown in Figure 55 (SEQ ID NO:150) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 20, a transmembrane domain from about amino acid 161 to about amino acid 179, an immunoglobulin-like fold from about amino acid 83 to about amino acid 127 and potential N-glycosylation sites from about amino acid 42 to about amino acid 45, from about amino acid 66 to about amino acid 69 and from about amino acid 74 to about amino acid 77. Clone UNQ326 (DNA45415-1318) has been deposited

with ATCC on April 28, 1998 and is assigned ATCC deposit no. 209810.

Analysis of the amino acid sequence of the full-length PRO386 polypeptide suggests that it possesses significant sequence similarity to the sodium channel beta-2 subunit, thereby indicating that PRO386 is a novel homolog thereof. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO386 amino acid sequence and the following Dayhoff sequences, A57843,

- 5 MYP0_HUMAN, GEN14531, JC4024, HS46KDA_1, HSU90716_1, D86996_2, MUSIGLVD_1, DMU42768_1 and S19247.

EXAMPLE 26: Isolation of cDNA Clones Encoding Human PRO540

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, 10 wherein the consensus sequence obtained is herein designated DNA39631. Based on the DNA39631 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO540.

Forward and reverse PCR primers were synthesized:

forward PCR primer 5'-CTGGGGCTACACACGGGGTGAGG-3' (SEQ ID NO:158)

15 reverse PCR primer 5'-GGTGCCGCTGCAGAAAGTAGAGCG-3' (SEQ ID NO:159)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40654 sequence which had the following nucleotide sequence

hybridization probe

5'-GCCCAAATGAAAACGGGCCCTACTTCCTGGCCCTCCGCGAGATG-3'

20 (SEQ ID NO:160)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO540 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

25 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO540 [herein designated as UNQ341 (DNA44189-1322)] (SEQ ID NO:156) and the derived protein sequence for PRO540.

The entire nucleotide sequence of UNQ341 (DNA44189-1322) is shown in Figure 58 (SEQ ID NO:156). Clone UNQ341 (DNA44189-1322) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 21-23 and ending at the stop codon at nucleotide positions 1257-1259 (Figure 58). The predicted polypeptide precursor is 412 amino acids long (Figure 59). The full-length PRO540 protein shown in Figure 59 has an estimated molecular weight of about 46,658 daltons and a pI of about 6.65. Important regions of the amino acid sequence of PRO540 include the signal peptide, potential N-glycosylation sites, a potential lipid substrate binding site, a sequence typical of lipases and serine proteins, and a beta-transducin family Trp-Asp repeat. Clone UNQ341 (DNA44189-1322) has been deposited with ATCC and is assigned ATCC deposit no. 209699.

35

EXAMPLE 27: Isolation of cDNA Clones Encoding Human PRO615

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA42240. Based on the DNA42240 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of

interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO615.

Forward and reverse PCR primers were synthesized:

forward PCR primer 5'-TGGTCTCGCCTTGATCGTGTCT-3' (SEQ ID NO:163)

forward PCR primer 5'-GTGTACTGAGCGCGGTTAG-3' (SEQ ID NO:164)

reverse PCR primer 5'-CTGAAGGTGATGGCTGCCCTCAC-3' (SEQ ID NO:165)

5 reverse PCR primer 5'-CCAGGAGGCTCATGGAAAGTCC-3' (SEQ ID NO:166)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA42240 sequence which had the following nucleotide sequence:

hybridization probe

5'-CCACGAGTCTAACGAGATGTACTGCGTGTCAACCGCAACGAGGATGCCT-3'

10 (SEQ ID NO:167)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO615 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human bone marrow tissue (LIB255).

15 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO615 [herein designated as UNQ352 (DNA48304-1323)] (SEQ ID NO:161) and the derived protein sequence for PRO615.

The entire nucleotide sequence of UNQ352 (DNA48304-1323) is shown in Figure 60 (SEQ ID NO:161). Clone UNQ352 (DNA48304-1323) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 51-53 and ending at the stop codon at nucleotide positions 723-725 (Figure 60). The predicted polypeptide precursor is 224 amino acids long (Figure 61). The full-length PRO615 protein shown in Figure 61 has an estimated molecular weight of about 24,810 daltons and a pI of about 4.75. Important regions of the amino acid sequence of PRO615 include a type II transmembrane domain, corresponding to about amino acids 24-43, other transmembrane domains, corresponding to about amino acids 74-90, 108-126, and 145-161, respectively, and a potential N-glycosylation site, corresponding to about amino acids 97-100. Clone UNQ352 (DNA48304-1323) has been deposited with ATCC and is assigned ATCC deposit no. 209811.

EXAMPLE 28: Isolation of cDNA Clones Encoding Human PRO618

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA30900. Based on the DNA30900 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO618.

Forward and reverse PCR primers were synthesized:

forward PCR primer 5'-TAACAGCTGCCACTGCTTCCAGG-3' (SEQ ID NO:171)

reverse PCR primer 5'-TAATCCAGCAGTGCAGGCCGG-3' (SEQ ID NO:172)

35 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA30900 sequence which had the following nucleotide sequence

hybridization probe

5'-ATGCCCTCCACGGTGCTGTGGACCCTGGCAAGGTGTGGCAGAA-3'

(SEQ ID NO:173)

Screening of the above described library gave rise to the partial cDNA clone designated herein DNA35597 (SEQ ID NO:170). Extension of this sequence using repeated cycles of BLAST and phrap gave rise to a nucleotide sequence designated herein as DNA43335. Primers based upon the DNA43335 consensus sequence were then prepared as follows.

forward PCR primer 5'-TGCCTATGCACTGAGGAGGCAGAAG-3' (SEQ ID NO:174)

5 reverse PCR primer 5'-AGGCAGGGACACAGAGTCCATTCAC-3' (SEQ ID NO:175)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA43335 sequence which had the following nucleotide sequence

hybridization probe

5'-AGTATGATTGCCGTGCACCCAGGGCCAGTGGACGATCCAGAACAGGAGG-3'

10 (SEQ ID NO:176)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate full length clones encoding the PRO618 gene using the second probe oligonucleotide and one of the second set of PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver tissue (LIB229).

15 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO618 [herein designated as UNQ354 (DNA49152-1324)] (SEQ ID NO:168) and the derived protein sequence for PRO618.

The entire nucleotide sequence of UNQ354 (DNA49152-1324) is shown in Figure 62 (SEQ ID NO:168). Clone UNQ354 (DNA49152-1324) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 73-75 and ending at the stop codon at nucleotide positions 2479-2481 (Figure 62). The predicted polypeptide precursor is 802 amino acids long (Figure 63). The full-length PRO618 protein shown in Figure 63 has an estimated molecular weight of about 88,846 daltons and a pI of about 6.41. Important regions of the amino acid sequence of PRO618 include type II transmembrane domain, a sequence typical of a protease, trypsin family, histidine active site, multiple N-glycosylation sites, two sequences typical of a Kringle domain, two regions having sequence similarity to Kallikrein light chain, and a region having sequence similarity to low-density lipoprotein receptor. Clone UNQ354 (DNA49152-1324) has been deposited with ATCC and is assigned ATCC deposit no. 209813.

EXAMPLE 29: Isolation of cDNA Clones Encoding Human PRO719

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, 30 wherein the consensus sequence obtained is herein designated DNA44851. Based on the DNA44851 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO719.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GTGAGCATGAGCGAGCCGTCCAC-3' (SEQ ID NO:179)

35 reverse PCR primer 5'-GCTATTACAACGGTTCTTGCAGC-3' (SEQ ID NO:180)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA44851 sequence which had the following nucleotide sequence

hybridization probe

5'-TTGACTCTGGTGAATCAGGACAAGCCGAGTTTGCCCTCCAG-3' (SEQ ID NO:181)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO719 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human placenta tissue (LIB90).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO719
5 [herein designated as UNQ387 (DNA49646-1327)] (SEQ ID NO:177) and the derived protein sequence for PRO719.

The entire nucleotide sequence of UNQ387 (DNA49646-1327) is shown in Figure 65 (SEQ ID NO:177). Clone UNQ387 (DNA49646-1327) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 223-225 and ending at the stop codon at nucleotide positions 1285-1287 (Figure 65). The predicted polypeptide precursor is 354 amino acids long (Figure 66). The full-length PRO719 protein shown in
10 Figure 66 has an estimated molecular weight of about 39,362 daltons and a pI of about 8.35. Analysis of the full length PRO719 sequence evidences the presence of a signal peptide from about amino acid 1 to about amino acid 16 as shown in Figure 66 (SEQ ID NO:178), a lipase-associated serine-containing active site at about amino acid 163 to about amino acid 172, and two potential N-glycosylation sites from about amino acid 80 to about amino acid 83 and about amino acid 136 to about amino acid 139. Clone UNQ387 (DNA49646-1327) has been deposited with
15 ATCC on March 26, 1998 and is assigned ATCC deposit no. 209705.

Analysis of the amino acid sequence of the full-length PRO719 polypeptide suggests that it possesses significant sequence similarity to the lipoprotein lipase H protein, thereby indicating that PRO719 may be a novel lipoprotein lipase homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO719 amino acid sequence and the following Dayhoff sequences,
20 LIPL_HUMAN, LIPH_HUMAN, D83548_1, A24059_1, P_R30740, D88666_1, A43357, A46696, B43357 and A49488.

EXAMPLE 30: Isolation of cDNA Clones Encoding Human PRO724

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above,
25 wherein the consensus sequence obtained is herein designated DNA35603. Based on the DNA35603 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO724.

Pairs of PCR primers (forward and reverse) were synthesized:

forward PCR primer 1 5'-GGCTGTCACTGTGGAGACAC-3' (SEQ ID NO:184)

30 forward PCR primer 2 5'-GCAAGGTCAATTACAGCTG-3' (SEQ ID NO:185)

reverse PCR primer 1 5'-AGAACATAGGAGCAGTCCCCTC-3' (SEQ ID NO:186)

reverse PCR primer 2 5'-TGCCTGCTGCTGCACAATCTCAG-3' (SEQ ID NO:187)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA35603 sequence which had the following nucleotide sequence

35 hybridization probe

5'-GGCTATTGCTTGCTGGACAGACCCTGTGGCTTAGGCTCTGGC-3' (SEQ ID NO:188)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO724 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of

the cDNA libraries was isolated from human fetal lung tissue (LIB26).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO724 [herein designated as UNQ389 (DNA49631-1328)] (SEQ ID NO:182) and the derived protein sequence for PRO724.

The entire nucleotide sequence of UNQ389 (DNA49631-1328) is shown in Figure 67 (SEQ ID NO:182). Clone UNQ389 (DNA49631-1328) contains a single open reading frame with an apparent translational initiation site 5 at nucleotide positions 546-548 and ending at the stop codon at nucleotide positions 2685-2687 (Figure 67). The predicted polypeptide precursor is 713 amino acids long (Figure 68). The full-length PRO724 protein shown in Figure 68 has an estimated molecular weight of about 76,193 daltons and a pI of about 5.42. Analysis of the full-length PRO724 amino acid sequence shown in Figure 68 (SEQ ID NO:183) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 16, a transmembrane domain from about amino acid 10 442 to about amino acid 462 and LDL receptor class A domain regions from about amino acid 152 to about amino acid 171, about amino acid 331 to about amino acid 350, about amino acid 374 to about amino acid 393 and about amino acid 411 to about amino acid 430. Clone UNQ389 (DNA49631-1328) has been deposited with ATCC on April 28, 1998 and is assigned ATCC deposit no. 209806

Analysis of the amino acid sequence of the full-length PRO724 polypeptide suggests that it possesses 15 significant sequence similarity to the human LDL receptor protein, thereby indicating that PRO724 may be a novel LDL receptor homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO724 amino acid sequence and the following Dayhoff sequences, P_R48547, MMAM2R_1, LRP2_RAT, P_R60517, P_R47861, P_R05533, A44513_1, A30363, P_R74692 and LMLIPOPHO_1.

20

EXAMPLE 31: Isolation of cDNA Clones Encoding Human PRO772

One cDNA sequence was isolated in the amylase screen described in Example 2, wherein that cDNA sequence is herein designated DNA43509 (see Figure 71). Based on the DNA43509 sequence, oligonucleotide probes were generated and used to screen a human fetal lung library (LIB25) prepared as described in paragraph 1 of 25 Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

A pair of PCR primers (forward and reverse) were synthesized based on the DNA43509 sequence:

forward PCR primer 5'-CGTTTGAGAACCTACTCAGGCAG-3' (SEQ ID NO:192)

reverse PCR primer 5'-CCTCCACCAACTGTCAATGTTGTGG-3' (SEQ ID NO:193)

30 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA43509 sequence which had the following nucleotide sequence

hybridization probe

5'-AAAGTGCTGCTGGTCTGCAGACGCGATGGATAACGT-3' (SEQ ID NO:194)

Using the above described primers and library, a full length clone was identified that contained a single open 35 reading frame with an apparent translational initiation site at nucleotide positions 131-133 and ending at the stop codon found at nucleotide positions 587-589 (Figure 69; SEQ ID NO:189). The predicted polypeptide precursor is 152 amino acids long, has a calculated molecular weight of approximately 17,170 daltons and an estimated pI of approximately 9.62. Analysis of the full-length PRO772 sequence shown in Figure 70 (SEQ ID NO:190) evidences the presence of the following: a potential type II transmembrane domain from about amino acid 26 to about amino

acid 42, other potential transmembrane domains from about amino acid 44 to about amino acid 65, from about amino acid 81 to about amino acid 101 and from about amino acid 109 to about amino acid 129, leucine zipper pattern sequences from about amino acid 78 to about amino acid 99 and from about amino acid 85 to about amino acid 106. Clone UNQ410 (DNA49645-1347) has been deposited with ATCC on April 28, 1998 and is assigned ATCC deposit no. 209809.

- 5 Analysis of the amino acid sequence of the full-length PRO772 polypeptide suggests that it possesses significant sequence similarity to the human A4 protein, thereby indicating that PRO772 may be a novel A4 protein homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO772 amino acid sequence and the following Dayhoff sequences, HSU93305_1, A4P_HUMAN, CELB0454_2, VPU_JSRV, CELC12D12_2, OCCM_AGRT1, LBPHIG1E_50, YIGK_ECOLI, 10 S76245 and P_R50807.

EXAMPLE 32: Isolation of cDNA Clones Encoding Human PRO852

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA34364. Based on the DNA34364 consensus 15 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO852.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 1 5'-CGCAGAAGCTACAGATTCTG-3' (SEQ ID NO:197)

forward PCR primer 2 5'-GGAAATTGGAGGCCAAAGC-3' (SEQ ID NO:198)

20 forward PCR primer 3 5'-GGATGTAGCCAGCAACTGTG-3' (SEQ ID NO:199)

forward PCR primer 4 5'-GCCTTGGCTCGTTCTCTTC-3' (SEQ ID NO:200)

forward PCR primer 5 5'-GGCCTGTGCCTGGATGG-3' (SEQ ID NO:201)

reverse PCR primer 1 5'-GACAAGACTACCTCCGTTGGC-3' (SEQ ID NO:202)

reverse PCR primer 2 5'-TGATGCACAGTTCACGCACCTGTTG-3' (SEQ ID NO:203)

25 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA34364 sequence which had the following nucleotide sequence

hybridization probe

5'-CGCTCCAAGGGCTTGACGTACAGTGAAGTACACACAAGGAAGCTG-3' (SEQ ID NO:204)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened 30 by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO852 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB228).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO852 [herein designated as UNQ418 (DNA45493-1349)] (SEQ ID NO:195) and the derived protein sequence for PRO852.

35 The entire nucleotide sequence of UNQ418 (DNA45493-1349) is shown in Figure 72 (SEQ ID NO:195). Clone UNQ418 (DNA45493-1349) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 94-96 and ending at the stop codon at nucleotide positions 16748-1650 (Figure 72). The predicted polypeptide precursor is 518 amino acids long (Figure 73). The full-length PRO852 protein shown in Figure 73 has an estimated molecular weight of about 56,180 daltons and a pI of about 5.08. Analysis of the full-

length PRO852 sequence shown in Figure 73 (SEQ ID NO:196) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 20, a transmembrane domain from about amino acid 466 to about amino acid 494, potential N-glycosylation sites from about amino acid 170 to about amino acid 173 and about amino acid 366 to about amino acid 369, leucine zipper sequence pattern blocks from about amino acid 10 to about amino acid 31 and from about amino acid 197 to about amino acid 218 and blocks of amino acids having sequence homology to eukaryotic and viral aspartyl proteases from about amino acid 109 to about amino acid 118, from about amino acid 252 to about amino acid 261 and from about amino acid 298 to about amino acid 310. Clone UNQ418 (DNA45493-1349) has been deposited with ATCC on April 28, 1998 and is assigned ATCC deposit no. 209805.

Analysis of the amino acid sequence of the full-length PRO852 polypeptide suggests that it possesses significant sequence similarity to various protease proteins, thereby indicating that PRO852 may be a novel protease protein or homolog thereof. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO852 amino acid sequence and the following Dayhoff sequences, PEPC_HUMAN, S66516, S66517, PEPE_CHICK, CATD_HUMAN, P_R74207, CARP_YEAST, PEP2_RABIT, CATE_HUMAN and RENI_MOUSE.

15 **EXAMPLE 33: Isolation of cDNA Clones Encoding Human PRO853**

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA43050. Based on the DNA43050 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO853.

20 Forward and reverse PCR primers were synthesized:

forward PCR primer 5'-CTTCATGGCCTTGGACTTGGCCAG-3' (SEQ ID NO:207)

reverse PCR primer 5'-ACGCCAGTGGCCTCAAGCTGGTTG-3' (SEQ ID NO:208)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA43050 sequence which had the following nucleotide sequence

25 hybridization probe

5'-CTTCTGAGCTTGAGCCACGGTTGGACATCCTCATCCACAATGC-3' (SEQ ID NO:209)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO853 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction 30 of the cDNA libraries was isolated from human fetal kidney tissue (LIB228).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO853 [herein designated as UNQ419 (DNA48227-1350)] (SEQ ID NO:205) and the derived protein sequence for PRO853.

The entire nucleotide sequence of UNQ419 (DNA48227-1350) is shown in Figure 74 (SEQ ID NO:205). Clone UNQ419 (DNA48227-1350) contains a single open reading frame with an apparent translational initiation site 35 at nucleotide positions 128-130 and ending at the stop codon at nucleotide positions 1259-1261 (Figure 74). The predicted polypeptide precursor is 377 amino acids long (Figure 75). The full-length PRO853 protein shown in Figure 75 has an estimated molecular weight of about 40,849 daltons and a pI of about 7.98. Important regions of the amino acid sequence of PRO853 include the signal peptide, corresponding to amino acids from about 1 to about 16 of SEQ ID NO:206, the glycosaminoglycan attachment site, corresponding to amino acids from about 46 to about

49 of SEQ ID NO:206, and two sequences typical of the short-chain alcohol dehydrogenase family, corresponding to amino acids from about 37 to about 49 and about 114 to about 124 of SEQ ID NO:206, respectively. Clone UNQ419 (DNA48227-1350) has been deposited with ATCC and is assigned ATCC deposit no. 209812.

EXAMPLE 34: Isolation of cDNA Clones Encoding Human PRO860

5 A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA38137. Based on the DNA38137 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO860.

Forward and reverse PCR primers were synthesized:

- 10 forward PCR primer 5'-GAAGGGACCTACATGTGTGTGGCC-3' (SEQ ID NO:212)
reverse PCR primer 5'-ACTGACCTTCCAGCTGAGCCACAC-3' (SEQ ID NO:213)
Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40654 sequence which had the following nucleotide sequence
hybridization probe
- 15 5'-AGGACTACACGGAGCCTGTGGAGCTTCTGGCTGTGCGAATTCAAGCTGGAA-3'
(SEQ ID NO:214)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO860 gene using the probe oligonucleotide and one of the PCR primers. RNA for 20 construction of the cDNA libraries was isolated from human fetal lung tissue (LIB26).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO860 [herein designated as UNQ421 (DNA41404-1352)] (SEQ ID NO:210) and the derived protein sequence for PRO860.

The entire nucleotide sequence of UNQ421 (DNA41404-1352) is shown in Figures 76A-B (SEQ ID NO:210). Clone UNQ421 (DNA41404-1352) contains a single open reading frame with an apparent translational 25 initiation site at nucleotide positions 58-60 and ending at the stop codon at nucleotide positions 3013-3015 (Figures 76A-B). The predicted polypeptide precursor is 985 amino acids long (Figure 77). The full-length PRO860 protein shown in Figure 77 has an estimated molecular weight of about 105,336 daltons and a pI of about 6.55. Important regions of the amino acid sequence of PRO860 include the transmembrane region corresponding to about amino acids 448-467, the extracellular domain, corresponding to amino acids about 1-447, several N-glycosylation sites, numerous 30 N-myristoylation sites and a sequence typical of phosphotyrosine interaction domain proteins.. Clone UNQ421 (DNA41404-1352) has been deposited with ATCC and is assigned ATCC deposit no. 209844.

EXAMPLE 35: Isolation of cDNA Clones Encoding Human PRO846

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, 35 wherein the consensus sequence obtained is herein designated DNA39949. Based on the DNA39949 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO846.

Forward and reverse PCR primers were synthesized:

forward PCR primer 5'-CCCTGCAGTGCACCTACAGGGAAG-3' (SEQ ID NO:217)

reverse PCR primer 5'-CTGTCTTCCCCTGCTGGCTGTGG-3' (SEQ ID NO:218)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA39949 sequence which had the following nucleotide sequence

hybridization probe

5'-GGTGCAGGAAGGGTGGGATCCTCTCTCGCTGCTCTGGCACATC-3'

5 (SEQ ID NO:219)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO846 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

10 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO846 [herein designated as UNQ422 (DNA44196-1353)] (SEQ ID NO:215) and the derived protein sequence for PRO846.

The entire nucleotide sequence of UNQ422 (DNA44196-1353) is shown in Figure 78 (SEQ ID NO:215). Clone UNQ422 (DNA44196-1353) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 25-27 and ending at the stop codon at nucleotide positions 1021-1023 (Figure 78). The 15 predicted polypeptide precursor is 332 amino acids long (Figure 79). The full-length PRO846 protein shown in Figure 79 has an estimated molecular weight of about 36,143 daltons and a pI of about 5.89. Important regions of the amino acid sequence of PRO846 include the signal peptide, the transmembrane domain, an N-glycosylation site, a sequence typical of fibrinogen beta and gamma chains C-terminal domain, and a sequence typical of Ig like V-type domain as shown in Figure 79. Clone UNQ422 (DNA44196-1353) has been deposited with ATCC and is assigned 20 ATCC deposit no. 209847.

EXAMPLE 36: Isolation of cDNA Clones Encoding Human PRO862

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA47370. Based on the DNA47370 consensus 25 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO862.

Forward and reverse PCR primers were synthesized:

forward PCR primer 5'GGGATCATGTTGGCCCTGGTC-3' (SEQ ID NO:222)

reverse PCR primer 5'-GCAAGGCAGACCCAGTCAGCCAG-3' (SEQ ID NO:223)

30 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA47370 sequence which had the following nucleotide sequence

hybridization probe

5'-CTGCCTGCTACCCTCCAAGTGAGGCCAAGCTCTACGGTCGTTGTG-3'

(SEQ ID NO:225)

35 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO862 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human pancreas tissue (LIB55).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO862 [herein designated as UNQ424 (DNA52187-1354)] (SEQ ID NO:220) and the derived protein sequence for PRO862.

The entire nucleotide sequence of UNQ424 (DNA52187-1354) is shown in Figure 80 (SEQ ID NO:220). Clone UNQ424 (DNA52187-1354) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 410-412 and ending at the stop codon at nucleotide positions 848-850 (Figure 80). The 5 predicted polypeptide precursor is 146 amino acids long (Figure 81). The full-length PRO862 protein shown in Figure 81 has an estimated molecular weight of about 16,430 daltons and a pI of about 5.05. Important regions of the amino acid sequence of PRO862 include the signal peptide, an N-myristoylation site, and sequences having similarity to region to Alpha-lactalbumin/lysozyme C proteins as shown in Figure 81. Clone UNQ424 (DNA52187-1354) has been deposited with the ATCC and is assigned ATCC deposit no. 209845.

10

EXAMPLE 37: Isolation of cDNA Clones Encoding Human PRO864

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA40666. Based on the DNA40666 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of 15 interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO864.

Forward and reverse PCR primers were synthesized:

forward PCR primer 5'-GCTGCAGCTGCAAATTCCACTGG-3' (SEQ ID NO:227)

reverse PCR primer 5'-TGGTGGGAGACTGTTAAATTATCGGCC-3' (SEQ ID NO:228)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40666 20 sequence which had the following nucleotide sequence

hybridization probe

5'-TGCTTCGTCAAGTGCCGGCAGTGCCAGCGGCCGTGGAGTT-3'

(SEQ ID NO:229)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened 25 by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO864 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal brain tissue (LIB153).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO864 [herein designated as UNQ426 (DNA48328-1355)] (SEQ ID NO:225) and the derived protein sequence for PRO864.

The entire nucleotide sequence of UNQ426 (DNA48328-1355) is shown in Figure 82 (SEQ ID NO:225). Clone UNQ426 (DNA48328-1355) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 37-39 and ending at the stop codon at nucleotide positions 1090-1092 (Figure 82). The predicted polypeptide precursor is 351 amino acids long (Figure 83). The full-length PRO864 protein shown in Figure 83 has an estimated molecular weight of about 39,052 and a pI of about 8.97. Important regions of the amino 35 acid sequence of PRO864 include the signal peptide, two N-glycosylation sites, a Wnt-1 family signature sequence, and sequence regions homologous to Wnt-1 family proteins as shown in Figure 83. Clone UNQ426 (DNA48328-1355) has been deposited with ATCC and is assigned ATCC deposit no. 209843.

EXAMPLE 38: Isolation of cDNA Clones Encoding Human PRO792

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA38106. Based on the DNA38106 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO792.

5 A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GCGAGAACTGTGTCATGATGCTGC-3' (SEQ ID NO:232)

reverse PCR primer 5'-GTTTCTGAGACTCAGCAGCGGTGG-3' (SEQ ID NO:233)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA38106 sequence which had the following nucleotide sequence

10 hybridization probe

5'-CACCGTGTGACAGCGAGAAGGACGGCTGGATCTGTGAGAAAAGGCACAAC-3' (SEQ ID NO:234)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO792 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of 15 the cDNA libraries was isolated from human bone marrow tissue (LIB255).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO792 [herein designated as UNQ431 (DNA56352-1358)] (SEQ ID NO:230) and the derived protein sequence for PRO792.

The entire nucleotide sequence of UNQ431 (DNA56352-1358) is shown in Figure 84 (SEQ ID NO:230). Clone UNQ431 (DNA56352-1358) contains a single open reading frame with an apparent translational initiation site 20 at nucleotide positions 67-69 and ending at the stop codon at nucleotide positions 946-948 (Figure 84). The predicted polypeptide precursor is 293 amino acids long (Figure 85). The full-length PRO792 protein shown in Figure 85 has an estimated molecular weight of about 32,562 daltons and a pI of about 6.53. Analysis of the full-length PRO792 sequence shown in Figure 85 (SEQ ID NO:231) evidences the presence of the following: a type II transmembrane domain from about amino acid 31 to about amino acid 54, potential N-glycosylation sites from about amino acid 73 25 to about amino acid 76 and from about amino acid 159 to about amino acid 162, a leucine zipper amino acid sequence pattern from about amino acid 102 to about amino acid 123, potential N-myristylation sites from about amino acid 18 to about amino acid 23, from about amino acid 133 to about amino acid 138 and from about amino acid 242 to about amino acid 247 and a C-type lectin domain signature block from about amino acid 264 to about amino acid 287. 30 Clone UNQ431 (DNA56352-1358) has been deposited with ATCC on May 6, 1998 and is assigned ATCC deposit no. 209846.

Analysis of the amino acid sequence of the full-length PRO792 polypeptide suggests that it possesses significant sequence similarity to the CD23 protein, thereby indicating that PRO792 may be a novel CD23 homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO792 amino acid sequence and the following Dayhoff sequences, S34198, A07100_1, A05303_1, 35 P_R41689, P_P82839, A10871_1, P_R12796, P_R47199, A46274 and P_R32188.

EXAMPLE 39: Isolation of cDNA Clones Encoding Human PRO866

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA44708. Based on the DNA44708 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO866.

PCR primers (forward and reverse) were synthesized:

- 5 forward PCR primer 1 5'-CAGCACTGCCAGGGAAAGAGGG-3' (SEQ ID NO:237)
- forward PCR primer 2 5'-CAGGACTCGCTACGTCCG-3' (SEQ ID NO:238)
- forward PCR primer 3 5'-CAGCCCCTTCTCCTCCTTCTCCC-3' (SEQ ID NO:239)
- reverse PCR primer 1 5'-GCAGTTATCAGGGACGCAGTCAGCC-3' (SEQ ID NO:240)
- reverse PCR primer 2 5'-CCAGCGAGAGGCAGATAG-3' (SEQ ID NO:241)
- 10 reverse PCR primer 3 5'-CGGTCACCCTGTCCTGCAGGGATG-3' (SEQ ID NO:242)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA44708 sequence which had the following nucleotide sequence

hybridization probe

5'-CAGCCCCTTCTCCTCCTTCTCCCACGTCTATCTGCCTCTC-3' (SEQ ID NO:243)

- 15 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO866 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB228).

- 20 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO866 [herein designated as UNQ435 (DNA53971-1359)] (SEQ ID NO:235) and the derived protein sequence for PRO866.

- The entire nucleotide sequence of UNQ435 (DNA53971-1359) is shown in Figure 86 (SEQ ID NO:235). Clone UNQ435 (DNA53971-1359) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 275-277 and ending at the stop codon at nucleotide positions 1268-1270 (Figure 86). The predicted polypeptide precursor is 331 amino acids long (Figure 87). The full-length PRO866 protein shown in
- 25 Figure 87 has an estimated molecular weight of about 35,844 daltons and a pI of about 5.45. Analysis of the full-length PRO866 sequence shown in Figure 87 (SEQ ID NO:236) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 26. Clone UNQ435 (DNA53971-1359) has been deposited with ATCC on April 7, 1998 and is assigned ATCC deposit no. 209750.

- 30 Analysis of the amino acid sequence of the full-length PRO866 polypeptide suggests that it possesses significant sequence similarity to the mindin/spondin family of proteins, thereby indicating that PRO866 may be a novel mindin homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO866 amino acid sequence and the following Dayhoff sequences, AB006085_1, AB006084_1, AB006086_1, AF017267_1, CWU42213_1, AC004160_1, CPMICRP_1, S49108, A48569 and I46687.

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EXAMPLE 40: Isolation of cDNA Clones Encoding Human PRO871

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA40324. Based on the DNA40324 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of

interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO871.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 1 5'-TGCAGGAGATCCTACTGGCACAGGG-3' (SEQ ID NO:246)

forward PCR primer 2 5'-CGAGTTAGTCAGAGCATG-3' (SEQ ID NO:247)

forward PCR primer 3 5'-CAGATGGTGTGCTGTTGCCG-3' (SEQ ID NO:248)

5 reverse PCR primer 1 5'-CAACTGGAACAGGAACAGATGTGGATC-3' (SEQ ID NO:249)

reverse PCR primer 2 5'-CTGGTTCAAGCAGTGCAAGGGTCTG-3' (SEQ ID NO:250)

reverse PCR primer 3 5'-CCTCTCCGATTAAAACGC-3' (SEQ ID NO:251)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40324 sequence which had the following nucleotide sequence

10 hybridization probe

5'-GAGAGGACTGGTTGCCATGGCAAATGCTGGTTCTCATGATAATGG-3' (SEQ ID NO:252)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO871 gene using the probe oligonucleotide and one of the PCR primers. RNA for 15 construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO871 [herein designated as UNQ438 (DNA50919-1361)] (SEQ ID NO:244) and the derived protein sequence for PRO871.

The entire nucleotide sequence of UNQ438 (DNA50919-1361) is shown in Figure 88 (SEQ ID NO:244). Clone UNQ438 (DNA50919-1361) contains a single open reading frame with an apparent translational initiation site 20 at nucleotide positions 191-193 and ending at the stop codon at nucleotide positions 1607-1609 (Figure 88). The predicted polypeptide precursor is 472 amino acids long (Figure 89). The full-length PRO871 protein shown in Figure 89 has an estimated molecular weight of about 53,847 daltons and a pI of about 5.75. Analysis of the full-length PRO871 sequence shown in Figure 89 (SEQ ID NO:245) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 21, potential N-glycosylation sites from about amino acid 109 25 to about amino acid 112 and from about amino acid 201 to about amino acid 204, a cyclophilin-type peptidy-prolyl cis-trans isomerase signature sequence from about amino acid 49 to about amino acid 66 and regions that are homologous to cyclophilin-type peptidy-prolyl cis-trans isomerases from about amino acid 96 to about amino acid 140, from about amino acid 49 to about amino acid 89 and from about amino acid 22 to about amino acid 51. Clone 30 UNQ438 (DNA50919-1361) has been deposited with ATCC on May 6, 1998 and is assigned ATCC deposit no. 209848.

Analysis of the amino acid sequence of the full-length PRO871 polypeptide suggests that it possesses significant sequence similarity to the cyclophilin family of proteins, thereby indicating that PRO871 may be a novel cyclophilin protein family member. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO871 amino acid sequence and the following Dayhoff sequences, 35 SPBC16H5_5, S64705, YAL5_SCHPO, CYP4_CAEEL, CELC34D4_7, CYPA_CAEEL, HUMORF006_1, CYPI_MYCTU, AF043642_1 and HSSRCYP_1.

EXAMPLE 41: Isolation of cDNA Clones Encoding Human PRO873

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA39621. Based on the DNA39621 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO873.

A pair of PCR primers (forward and reverse) were synthesized:

5 forward PCR primer 5'-AGGTGCCTGCAGGAGTCCTGGGG-3' (SEQ ID NO:255)

reverse PCR primer 5'- CCACCTCAGGAAGCCGAAGATGCC-3' (SEQ ID NO:256)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA39621 sequence which had the following nucleotide sequence:

hybridization probe

10 5'-GAACGGTACAAGTGGCTCGCCTTCAGCGAGGACTGTCTGTACCTG-3' (SEQ ID NO:257)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO873 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver tissue (LIB229).

15 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO873 [herein designated as UNQ440 (DNA44179-1362)] (SEQ ID NO:253) and the derived protein sequence for PRO873.

The entire nucleotide sequence of UNQ440 (DNA44179-1362) is shown in Figure 90 (SEQ ID NO:253). Clone UNQ440 (DNA44179-1362) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 139-141 and ending at the stop codon at nucleotide positions 1774-1776 (Figure 90). The predicted polypeptide precursor is 545 amino acids long (Figure 91). The full-length PRO873 protein shown in Figure 91 has an estimated molecular weight of about 58,934 daltons and a pI of about 9.45. Analysis of the full-length PRO873 sequence shown in Figure 91 (SEQ ID NO:254) evidences the presence of the following features: a signal peptide from about amino acid 1 to about amino acid 29; a carboxylesterase type-B serine active site at about amino acid 312 to about amino acid 327; a carboxylesterase type-B signature 2 motif at about amino acid 218 to about amino acid 228; and three potential N-glycosylation sites at about amino acid 318 to about amino acid 321, about amino acid 380 to about amino acid 383, and about amino acid 465 to about amino acid 468. Clone UNQ440 (DNA44179-1362) has been deposited with ATCC on May 6, 1998 and is assigned ATCC deposit no. 209851.

Analysis of the amino acid sequence of the full-length PRO873 polypeptide suggests that it possesses significant sequence similarity to a human liver carboxylesterase, thereby indicating that PRO873 may be a novel carboxylesterase. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO873 amino acid sequence and the following Dayhoff sequences: ES10_RAT, GEN12405, AB010633_1, EST4_RAT, A48809, SASB_ANAPL, RNU41662_1, RNU22952_1, BAL_RAT, GEN13522.

35 **EXAMPLE 42: Isolation of cDNA Clones Encoding Human PRO940**

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA47442. Based on the DNA47442 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO940.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CAAAGCCTGCGCTGGTCTGTG-3' (SEQ ID NO:260)

reverse PCR primer 5'-TTCTGGAGCCCAGAGGGTGCTGAG-3' (SEQ ID NO:262)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA47442 sequence which had the following nucleotide sequence

5 hybridization probe

5'-GGAGCTGCCACCCATTCAAATGGAGCACGAAGGAGAGTTCACCTG-3' (SEQ ID NO:263)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO940 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of 10 the cDNA libraries was isolated from human fetal liver tissue (LIB229).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO940 [herein designated as UNQ477 (DNA54002-1367)] (SEQ ID NO:258) and the derived protein sequence for PRO940.

The entire nucleotide sequence of UNQ477 (DNA54002-1367) is shown in Figure 92 (SEQ ID NO:258). Clone UNQ477 (DNA54002-1367) contains a single open reading frame with an apparent translational initiation site 15 at nucleotide positions 46-48 and ending at the stop codon at nucleotide positions 1678-1680 (Figure 92). The predicted polypeptide precursor is 544 amino acids long (Figure 93). The full-length PRO940 protein shown in Figure 93 has an estimated molecular weight of about 60,268 daltons and a pI of about 9.53. Analysis of the full-length PRO940 sequence shown in Figure 93 (SEQ ID NO:259) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 15, potential N-glycosylation sites from about amino acid 100 20 to about amino acid 103, from about amino acid 297 to about amino acid 300 and from about amino acid 306 to about amino acid 309 and an immunoglobulin and major histocompatibility complex signature sequence block from about amino acid 365 to about amino acid 371. Clone UNQ477 (DNA54002-1367) has been deposited with ATCC on April 7, 1998 and is assigned ATCC deposit no. 209754.

Analysis of the amino acid sequence of the full-length PRO940 polypeptide suggests that it possesses 25 significant sequence similarity to CD33 and the OB binding protein-2. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO940 amino acid sequence and the following Dayhoff sequences, CD33_HUMAN, HSU71382_1, HSU71383_1, D86359_1, PGBM_HUMAN, MAGS_MOUSE, D86983_1, C22B_HUMAN, P_W01002 and HVU24116_1.

30 EXAMPLE 43: Isolation of cDNA Clones Encoding Human PRO941

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA35941. An EST sequence proprietary to Genentech was employed in the assembly and is herein designated DNA6415 (Figure 96; SEQ ID NO:265). Based 35 on the DNA35941 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO941.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CTTGACTGTCTCTGAATCTGCACCC-3' (SEQ ID NO:266)

reverse PCR primer 5'-AAGTGGTGGAAAGCCTCCAGTGTGG-3' (SEQ ID NO:267)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA35941 sequence which had the following nucleotide sequence

hybridization probe

5'-CCACTACGGTATTAGAGCAAAAGTTAAAACCATGGTTCCTGGAGCAGC-3' (SEQ ID NO:268)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened
5 by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO941 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO941 [herein designated as UNQ478 (DNA53906-1368)] (SEQ ID NO:263) and the derived protein sequence for PRO941.

10 The entire nucleotide sequence of UNQ478 (DNA53906-1368) is shown in Figure 94 (SEQ ID NO:263). Clone UNQ478 (DNA53906-1368) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 37-39 and ending at the stop codon at nucleotide positions 2353-2355 (Figure 94). The predicted polypeptide precursor is 772 amino acids long (Figure 95). The full-length PRO941 protein shown in Figure 95 has an estimated molecular weight of about 87,002 daltons and a pI of about 4.64. Analysis of the full-
15 length PRO941 sequence shown in Figure 95 (SEQ ID NO:264) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 21, potential N-glycosylation sites from about amino acid 57 to about amino acid 60, from about amino acid 74 to about amino acid 77, from about amino acid 419 to about amino acid 422, from about amino acid 437 to about amino acid 440, from about amino acid 508 to about amino acid 511, from about amino acid 515 to about amino acid 518, from about amino acid 516 to about amino acid 519 and from
20 about amino acid 534 to about amino acid 537, and cadherin extracellular repeated domain signature sequences from about amino acid 136 to about amino acid 146 and from about amino acid 244 to about amino acid 254. Clone UNQ478 (DNA53906-1368) has been deposited with ATCC on April 7, 1998 and is assigned ATCC deposit no. 209747.

Analysis of the amino acid sequence of the full-length PRO941 polypeptide suggests that it possesses
25 significant sequence similarity to a cadherin protein, thereby indicating that PRO941 may be a novel cadherin protein family member. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO941 amino acid sequence and the following Dayhoff sequences, I50180, CADA_CHICK, I50178, GEN12782, CADC_HUMAN, P_W25637, A38992, P_R49731, D38992 and G02678.

30 EXAMPLE 44: Isolation of cDNA Clones Encoding Human PRO944

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA47374. A variety of proprietary Genentech EST sequences were employed in the assembly and are shown in Figures 99-107. Based on the DNA47374 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of
35 interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO944.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CGAGCGAGTCATGGCCAACGC-3' (SEQ ID NO:280)

reverse PCR primer 5'-GTGTCACACGTAGTCTTCCCGCTGG-3' (SEQ ID NO:281)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA47374 sequence which had the following nucleotide sequence

hybridization probe

5'-CTGCAGCTGTTGGCTTCATTCTGCCTCCTGGATGGATCG-3' (SEQ ID NO:282)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened 5 by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO944 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO944 [herein designated as UNQ481 (DNA52185-1370)] (SEQ ID NO:269) and the derived protein sequence for PRO944.

10 The entire nucleotide sequence of UNQ481 (DNA52185-1370) is shown in Figure 97 (SEQ ID NO:269). Clone UNQ481 (DNA52185-1370) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 219-221 and ending at the stop codon at nucleotide positions 852-854 (Figure 97). The predicted polypeptide precursor is 211 amino acids long (Figure 98). The full-length PRO944 protein shown in Figure 98 has an estimated molecular weight of about 22,744 daltons and a pI of about 8.51. Analysis of the full- 15 length PRO944 sequence shown in Figure 98 (SEQ ID NO:270) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 21, transmembrane domains from about amino acid 82 to about amino acid 102, from about amino acid 118 to about amino acid 142 and from about amino acid 161 to about amino acid 187, a potential N-glycosylation site from about amino acid 72 to about amino acid 75, a sequence block having homology to PMP-22/EMP/MP20 family of proteins from about amino acid 70 to about amino acid 111 and a 20 sequence block having homology to ABC-2 type transport system integral membrane protein from about amino acid 119 to about amino acid 133. Clone UNQ481 (DNA52185-1370) has been deposited with ATCC on May 14, 1998 and is assigned ATCC deposit no. 209861.

Analysis of the amino acid sequence of the full-length PRO944 polypeptide suggests that it possesses significant sequence similarity to the CPE-R protein, thereby indicating that PRO944 may be a novel CPE-R 25 homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO944 amino acid sequence and the following Dayhoff sequences, AB000713_1, AB000714_1, AF035814_1, AF000959_1, HSU89916_1, EMP2_HUMAN, JC5732, CELF53B3_6, PM22_MOUSE and CGU49797_1.

30 **EXAMPLE 45: Isolation of cDNA Clones Encoding Human PRO983**

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA47473. Various proprietary Genentech EST sequences were employed in the assembly, wherein those EST sequences are shown in Figures 110-116. Based on the DNA47473 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that 35 contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO983.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GCACCACCGTAGGTACTTGTGTGAGGC-3' (SEQ ID NO:292)

reverse PCR primer 5'-AACCAACCAGAGCCAAGAGGCCGGG -3' (SEQ ID NO:293)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA47473 sequence which had the following nucleotide sequence

hybridization probe

5'-CAGCGGAATCATCGATGCAGGGGCCTCAATTAATGTATCTGTGATGTTAC-3' (SEQ ID NO:294)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened
5 by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO983 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human bone marrow (LIB256).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO983 [herein designated as UNQ484 (DNA53977-1371)] (SEQ ID NO:283) and the derived protein sequence for PRO983.

10 The entire nucleotide sequence of UNQ484 (DNA53977-1371) is shown in Figure 108 (SEQ ID NO:283). Clone UNQ484 (DNA53977-1371) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 234-236 and ending at the stop codon at nucleotide positions 963-965 (Figure 108). The predicted polypeptide precursor is 243 amino acids long (Figure 109). The full-length PRO983 protein shown in Figure 109 has an estimated molecular weight of about 27,228 daltons and a pI of about 7.43. Analysis of the full-
15 length PRO983 sequence shown in Figure 109 (SEQ ID NO:284) evidences the presence of the following features: a putative transmembrane domain from about amino acid 224 to about amino acid 239; a potential N-glycosylation site from about amino acid 68 to about amino acid 71; and three potential N-myristoylation sites from about amino acid 59 to about amino acid 64, from about amino acid 64 to about amino acid 69, and from about amino acid 235 to about amino acid 240. Clone UNQ484 (DNA53977-1371) has been deposited with ATCC on May 14, 1998 and
20 is assigned ATCC deposit no. 209862.

Analysis of the amino acid sequence of the full-length PRO983 polypeptide suggests that it possesses significant sequence similarity to the vesicle-associated protein, VAP-33, thereby indicating that PRO983 may be a novel vesicle associated membrane protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO983 amino acid sequence and the following Dayhoff sequences: VP33_APLCA, CELF33D11_12, CELF42G2_2, S50623, YDFC_SCHPO, CELF54H5_2, CELZC196_8, CEF57A10_3, MSP3_GLORO, CEC15H11_1.

EXAMPLE 46: Isolation of cDNA Clones Encoding Human PRO1057

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above,
30 wherein the consensus sequence obtained is herein designated DNA49808. Based on the DNA49808 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1057.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GCATCTGCAGGAGAGAGCGAAGGG-3' (SEQ ID NO:297)

35 reverse PCR primer 5'-CATCGTCCCCGTGAATCCAGAGGC-3' (SEQ ID NO:298)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA49808 sequence which had the following nucleotide sequence

hybridization probe

5'-GAAGGGAGGCCCTTCAGTGGACCCGGGTCAAGAATAACCAC-3' (SEQ ID NO:299)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1057 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1057
5 [herein designated as UNQ522 (DNA57253-1382)] (SEQ ID NO:295) and the derived protein sequence for PRO1057.

The entire nucleotide sequence of UNQ522 (DNA57253-1382) is shown in Figure 117 (SEQ ID NO:295). Clone UNQ522 (DNA57253-1382) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 275-277 and ending at the stop codon at nucleotide positions 1514-1516 (Figure 117). The predicted polypeptide precursor is 413 amino acids long (Figure 118). The full-length PRO1057 protein shown in
10 Figure 118 has an estimated molecular weight of about 47,070 daltons and a pI of about 9.92. Analysis of the full-length PRO1057 sequence shown in Figure 118 (SEQ ID NO:296) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 16, potential N-glycosylation sites from about amino acid 90 to about amino acid 93, from about amino acid 110 to about amino acid 113 and from about amino acid 193 to about
15 amino acid 196, a glycosaminoglycan attachment site from about amino acid 236 to about amino acid 239 and a serine protease histidine-containing active site from about amino acid 165 to about amino acid 170. Clone UNQ522 (DNA57253-1382) has been deposited with ATCC on May 14, 1998 and is assigned ATCC deposit no. 209867.

Analysis of the amino acid sequence of the full-length PRO1057 polypeptide suggests that it possesses significant sequence similarity to various protease proteins, thereby indicating that PRO1057 may be a novel protease. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology
20 between the PRO1057 amino acid sequence and the following Dayhoff sequences, TRY_E_DROER, P_R14159, A69660, EBN1_EBV, S65494, GEN12688, A51084_1, P_R99571, A57514 and AF003200_1.

EXAMPLE 47: Isolation of cDNA Clones Encoding Human PRO1071

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above,
25 wherein the consensus sequence obtained is herein designated DNA53035. Based on the DNA53035 consensus sequence, it was determined that that consensus sequence shared significant sequence identity with Incyte EST clone no. 2872569, a clone that upon review appeared to encode a full length protein. As such, Incyte EST clone no. 2872569 was purchased and its insert was obtained and sequenced so as to confirm the proper sequence. This sequence is herein designated UNQ528 or DNA58847-1383.

30 DNA sequencing of the clone isolated as described above gave the full-length DNA sequence for PRO1071 [herein designated as UNQ528 (DNA58847-1383)] (SEQ ID NO:300) and the derived protein sequence for PRO1071.

The entire nucleotide sequence of UNQ528 (DNA58847-1383) is shown in Figure 119 (SEQ ID NO:300). Clone UNQ528 (DNA58847-1383) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 133-135 and ending at the stop codon at nucleotide positions 1708-1710 (Figure 119). The predicted polypeptide precursor is 525 amino acids long (Figure 120). The full-length PRO1071 protein shown in
35 Figure 120 has an estimated molecular weight of about 58,416 daltons and a pI of about 6.62. Analysis of the full-length PRO1071 sequence shown in Figure 120 (SEQ ID NO:301) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 25, a potential N-glycosylation site from about amino acid 251 to about amino acid 254, a thrombospondin-1 homology block from about amino acid 385 to about amino acid 399

and von Willibrands factor type C homology blocks from about amino acid 385 to about amino acid 399, from about amino acid 445 to about amino acid 459 and from about amino acid 42 to about amino acid 56. Clone UNQ528 (DNA58847-1383) has been deposited with ATCC on May 20, 1998 and is assigned ATCC deposit no. 209879.

Analysis of the amino acid sequence of the full-length PRO1071 polypeptide suggests that it possesses significant sequence similarity to the thrombospondin protein, thereby indicating that PRO1071 may be a novel 5 thrombospondin homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO1071 amino acid sequence and the following Dayhoff sequences, AB002364_1, D67076_1, BTPCINPGN_1, CET13H10_1, CEF25H8_5, CEF53B6_2, CEC26C6_6, HSSEMG_1, CET21B6_4 and BTY08561_1.

10 **EXAMPLE 48: Isolation of cDNA Clones Encoding Human PRO1072**

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA53125. Based on the DNA53125 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1072.

15 PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CCAGGAAATGCTCCAGGAAGAGCC-3' (SEQ ID NO:305)

reverse PCR primer 5'-GCCCATGACACCAAATTGAAGAGTGG-3' (SEQ ID NO:306)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA53125 sequence which had the following nucleotide sequence

20 hybridization probe

5'-AACGCAGGGATCTTCCAGTGCCCTTACATGAAGACTGAAGATGGG-3' (SEQ ID NO:307)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1072 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of 25 the cDNA libraries was isolated from human fetal lung tissue (LIB26).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1072 [herein designated as UNQ529 (DNA58747-1384)] (SEQ ID NO:302) and the derived protein sequence for PRO1072.

The entire nucleotide sequence of UNQ529 (DNA58747-1384) is shown in Figure 121 (SEQ ID NO:302). Clone UNQ529 (DNA58747-1384) contains a single open reading frame with an apparent translational initiation site 30 at nucleotide positions 65-67 and ending at the stop codon at nucleotide positions 1073-1075 (Figure 121). The predicted polypeptide precursor is 336 amino acids long (Figure 122). The full-length PRO1072 protein shown in Figure 122 has an estimated molecular weight of about 36,865 daltons and a pI of about 9.15. Analysis of the full-length PRO1072 sequence shown in Figure 122 (SEQ ID NO:303) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 21, short-chain alcohol dehydrogenase protein homology blocks 35 from about amino acid 134 to about amino acid 144, from about amino acid 44 to about amino acid 56 and from about amino acid 239 to about amino acid 248 and potential N-glycosylation sites from about amino acid 212 to about amino acid 215 and from about amino acid 239 to about amino acid 242. Clone UNQ529 (DNA58747-1384) has been deposited with ATCC on May 14, 1998 and is assigned ATCC deposit no. 209868.

Analysis of the amino acid sequence of the full-length PRO1072 polypeptide suggests that it possesses significant sequence similarity to the reductase family of proteins, thereby indicating that PRO1072 may be a novel reductase. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO1072 amino acid sequence and the following Dayhoff sequences, P_W03198, P_W15759, P_R60800, MTV037_3, CEC15H11_6, ATAC00234314, MTV022_13, SCU43704_1, OXIR_STRAT AND 5 CELC01G8_3.

EXAMPLE 49: Isolation of cDNA Clones Encoding Human PRO1075

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA34363. Based on the DNA34363 sequence, 10 oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1075.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-TGAGAGGCCTCTGGAAAGTTG-3' (SEQ ID NO:312)
forward PCR primer 5'-GTCAGCGATCAGTGAAAGC-3' (SEQ ID NO:313)
15 forward PCR primer 5'-CCAGAACGAAAGTAGCTCGGC-3' (SEQ ID NO:314)
forward PCR primer 5'-CCGACTAAAATGCATTGTC-3' (SEQ ID NO:315)
forward PCR primer 5'-CATTTGGCAGGAATTGTCC-3' (SEQ ID NO:316)
forward PCR primer 5'-GGTGCTATAAGGCCAAGGG-3' (SEQ ID NO:317)
reverse PCR primer 5'-CTGTATCTCTGGGCTATGTCAGAG-3' (SEQ ID NO:318)
20 reverse PCR primer 5'-CTACATATAATGGCACATGTCAGCC-3' (SEQ ID NO:319)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA34363 sequence which had the following nucleotide sequence

hybridization probe

5'-CGTCTTCCTATCCTAACCGACCTCAGATGCTCCCTCTGCTCCTG-3' (SEQ ID NO:320)

25 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1075 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human skin tumor tissue (LJB324).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1075 30 [herein designated as UNQ532 (DNA57689-1385)] (SEQ ID NO:308) and the derived protein sequence for PRO1075.

The entire nucleotide sequence of UNQ532 (DNA57689-1385) is shown in Figure 124 (SEQ ID NO:308). Clone UNQ532 (DNA57689-1385) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 137-139 and ending at the stop codon at nucleotide positions 1355-1357 (Figure 124). The predicted polypeptide precursor is 406 amino acids long (Figure 125). The full-length PRO1075 protein shown in 35 Figure 125 has an estimated molecular weight of about 46,927 daltons and a pI of about 5.21. Analysis of the full-length PRO1075 sequence shown in Figure 125 (SEQ ID NO:309) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 29, an endoplasmic reticulum targeting sequence from about amino acid 403 to about amino acid 406, a tyrosine kinase phosphorylation site from about amino acid 203 to about amino acid 211 and a sequence block having homology to the thioredoxin family of proteins from about amino acid

50 to about amino acid 66. Clone UNQ532 (DNA57689-1385) has been deposited with ATCC on May 14, 1998 and is assigned ATCC deposit no. 209869.

Analysis of the amino acid sequence of the full-length PRO1075 polypeptide suggests that it possesses significant sequence similarity to protein disulfide isomerase, thereby indicating that PRO1075 may be a novel protein disulfide isomerase. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced 5 significant homology between the PRO1075 amino acid sequence and the following Dayhoff sequences, CELC30H7_2, CELC06A6_3, CELF42G8_3, SS7942, ER72_CAEEL, CELC07A12_3, CEH06O01_4 and P_R51696.

EXAMPLE 50: Isolation of cDNA Clones Encoding Human PRO181

10 A cDNA sequence isolated in the amylase screen described in Example 2 above was found, by BLAST and FastA sequence alignment, to have sequence homology to a nucleotide sequence encoding the cornichon protein. This cDNA sequence is herein designated DNA13242 (Figure 130; SEQ ID NO:323). Based on the sequence homology, oligonucleotide probes were generated from the sequence of the DNA13242 molecule and used to screen a human placenta (LIB89) library prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B 15 (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

The oligonucleotide probes employed included:

forward PCR primer 5'-GTGCAGCAGAGTGGCTTACA-3' (SEQ ID NO:326)

reverse PCR primer 5'-ACTGGACCAATTCTTCTGTG-3' (SEQ ID NO:327)

20 hybridization probe

5'-GATATTCTAGCATATTGTCAGAAGGAAGGATGGTGCAAATTAGCT-3' (SEQ ID NO:328)

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 14-16 and ending at the stop codon found at nucleotide positions 446-448 (Figure 128; SEQ ID NO:321). The predicted polypeptide precursor is 144 amino acids long, has a calculated molecular 25 weight of approximately 16,699 daltons and an estimated pI of approximately 5.6. Analysis of the full-length PRO181 sequence shown in Figure 129 (SEQ ID NO:322) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 20, a putative type II transmembrane domain from about amino acid 11 to about amino acid 31 and other transmembrane domains from about amino acid 57 to about amino acid 77 and from about amino acid 123 to about amino acid 143. Clone UNQ155 (DNA23330-1390) has been deposited with ATCC on April 30, 14, 1998 and is assigned ATCC deposit no. 209775.

Analysis of the amino acid sequence of the full-length PRO181 polypeptide suggests that it possesses significant sequence similarity to the cornichon protein, thereby indicating that PRO181 may be a novel cornichon homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO181 amino acid sequence and the following Dayhoff sequences, AF022811_1, 35 CET09E8_3, S64058, YGF4_YEAST, YB60_YEAST, EBU89455_1, SIU36383_3 and PH1371.

EXAMPLE 51: Isolation of cDNA Clones Encoding Human PRO195

A cDNA sequence was isolated in the amylase screen described in Example 2 above and is herein designated DNA13199 (Figure 134; SEQ ID NO:332). The DNA13199 sequence was then compared to a variety

of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., *Methods in Enzymology* 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington; 5 <http://bozeman.mbt.washington.edu/phrap.docs/phrap.html>). The consensus sequence obtained therefrom is herein designated as DNA22778.

Based on the DNA22778 sequence, oligonucleotide probes were generated and used to screen a human placenta library (LIB89) prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 10 (1991)), and the cDNA size cut was less than 2800 bp.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-ACAAGCTGAGCTGCTGTGACAG-3' (SEQ ID NO:333)

reverse PCR primer 5'-TGATTCTGGCAACCAAGATGGC-3' (SEQ ID NO:334)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA22778 sequence which 15 had the following nucleotide sequence

hybridization probe

5'-ATGGCCTTGGCCGGAGGTTCGGGGACCGCTTCGGCTGAAG-3' (SEQ ID NO:335)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones 20 encoding the PRO195 gene using the probe oligonucleotide and one of the PCR primers.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 70-72 and ending at the stop codon found at nucleotide positions 1039-1041 (Figure 132; SEQ ID NO:330). The predicted polypeptide precursor is 323 amino acids long, has a calculated molecular weight of approximately 36,223 daltons and an estimated pI of approximately 5.06. Analysis of the full-length PRO195 sequence shown in Figure 132 (SEQ ID NO:330) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 31, a transmembrane domain from about amino acid 241 to 25 about amino acid 260 and a potential N-glycosylation site from about amino acid 90 to about amino acid 93. Clone UNQ169 (DNA26847-1395) has been deposited with ATCC on April 14, 1998 and is assigned ATCC deposit no. 209772.

30 Analysis of the amino acid sequence of the full-length PRO195 polypeptide suggests that it possesses no significant sequence similarity to any known protein. However, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO195 amino acid sequence and the following Dayhoff sequences, P_P91380, AF035118_1, HUMTROPCS_1, NUOD_SALTY and E70002.

35 **EXAMPLE 52: Isolation of cDNA Clones Encoding Human PRO865**

A cDNA sequence isolated in the amylase screen described in Example 2 above was herein designated DNA37642 (Figure 137, SEQ ID NO:338). The DNA37642 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologies therebetween. The homology

search was performed using the computer program BLAST or BLAST2 (Altshul et al., *Methods in Enzymology* 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington; <http://bozeman.mbt.washington.edu/phrap.docs/phrap.html>). The consensus sequence obtained is herein designated 5 DNA48615.

Based on the DNA48615 consensus sequence, probes were generated and used to screen a human fetal kidney (LJB227) library prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

10 PCR primers (forward and reverse) were synthesized:

forward PCR primer 1 5'-AAGCTGCCGGAGCTGCAATG-3' (SEQ ID NO:339)

forward PCR primer 2 5'-TTGCTTCTTAATCCTGAGCGC-3' (SEQ ID NO:340)

forward PCR primer 3 5'-AAAGGAGGACTTCGACTGC-3' (SEQ ID NO:341)

reverse PCR primer 1 5'-AGAGATTCCACTGCTCCAAGTCG-3' (SEQ ID NO:342)

15 reverse PCR primer 2 5'-TGTCCAGAACAGGCACATATCAGC-3' (SEQ ID NO:343)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA48615 sequence which had the following nucleotide sequence

hybridization probe

5'-AGACAGCGGACAGAGGTGCTTCTGCCAGGTTAGTGGTTACTTGGATGAT-3' (SEQ ID NO:344)

20 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO865 gene using the probe oligonucleotide and one of the PCR primers.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 173-175 and ending at the stop codon found at nucleotide positions 1577-1579 (Figure 135; SEQ ID NO:336). The predicted polypeptide precursor is 468 amino acids long, has a calculated molecular weight of approximately 54,393 daltons and an estimated pI of approximately 5.63. Analysis of the full-length PRO865 sequence shown in Figure 136 (SEQ ID NO:337) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 23, potential N-glycosylation sites from about amino acid 280 to about amino acid 283 and from about amino acid 384 to about amino acid 387, a potential amidation site from about amino acid 94 to about amino acid 97, glycosaminoglycan attachment sites from about amino acid 20 to about amino acid 23 and from about amino acid 223 to about amino acid 226, an aminotransferase class-V pyridoxyl-phosphate amino acid sequence block from about amino acid 216 to about amino acid 222 and an amino acid sequence block similar to that found in the interleukin-7 protein from about amino acid 338 to about amino acid 343. Clone 30 UNQ434 (DNA53974-1401) has been deposited with ATCC on April 14, 1998 and is assigned ATCC deposit no. about amino acid 94 to about amino acid 97, glycosaminoglycan attachment sites from about amino acid 20 to about amino acid 23 and from about amino acid 223 to about amino acid 226, an aminotransferase class-V pyridoxyl-phosphate amino acid sequence block from about amino acid 216 to about amino acid 222 and an amino acid sequence block similar to that found in the interleukin-7 protein from about amino acid 338 to about amino acid 343. Clone 35 UNQ434 (DNA53974-1401) has been deposited with ATCC on April 14, 1998 and is assigned ATCC deposit no. 209774.

Analysis of the amino acid sequence of the full-length PRO865 polypeptide suggests that it possesses no significant sequence similarity to any known protein. However, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO865 amino acid sequence and the following Dayhoff sequences, YMNO_YEAST, ATFCA4_43, S44168, P_W14549 and RABTCRG4_1.

EXAMPLE 53: Isolation of cDNA Clones Encoding Human PRO827

A cDNA sequence isolated in the amylase screen described in Example 2 above was found, by BLAST and FastA sequence alignment, to have sequence homology to nucleotide sequences encoding various integrin proteins. This cDNA sequence is herein designated DNA47751 (see Figure 140; SEQ ID NO:347). Based on the sequence homology, probes were generated from the sequence of the DNA47751 molecule and used to screen a human fetal pigment epithelium library (LIB113) prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

5 PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-AGGGACAGAGGCCAGAGGACTTC-3' (SEQ ID NO:348)
10 reverse PCR primer 5'-CAGGTGCATATTCACAGCAGGATG-3' (SEQ ID NO:349)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA47751 sequence which had the following nucleotide sequence

hybridization probe
15 5'-GGAACCTCCCTTCGTCACTCACCTGTTCTGCCCCCTGGTGTTCCT-3' (SEQ ID NO:350)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO827 gene using the probe oligonucleotide and one of the PCR primers.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 134-136 and ending at the stop codon found at nucleotide positions 506-508 (Figure 138; SEQ ID NO:345). The predicted polypeptide precursor is 124 amino acids long, has a calculated molecular weight of approximately 13,352 daltons and an estimated pI of approximately 5.99. Analysis of the full-length PRO827 sequence shown in Figure 139 (SEQ ID NO:346) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 22, a cell attachment sequence from about amino acid 70 to 25 about amino acid 72, a potential N-glycosylation site from about amino acid 98 to about amino acid 101 and an integrin alpha chain protein homology sequence from about amino acid 67 to about amino acid 81. Clone UNQ468 (DNA57039-1402) has been deposited with ATCC on April 14, 1998 and is assigned ATCC deposit no. 209777.

Analysis of the amino acid sequence of the full-length PRO827 polypeptide suggests that it possesses significant sequence similarity to the VLA-2 integrin protein and various other integrin proteins, thereby indicating 30 that PRO827 may be a novel integrin or splice variant thereof. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO240 amino acid sequence and the following Dayhoff sequences, S44142, ITA2_HUMAN, ITA1_RAT, ITA1_HUMAN, ITA4_HUMAN, ITA9_HUMAN, AF032108_1, ITAM_MOUSE, ITA8_CHICK and ITA6_CHICK.

35 **EXAMPLE 54: Isolation of cDNA Clones Encoding Human PRO1114**

A cDNA sequence isolated in the amylase screen described in Example 2 was found, by the WU-BLAST2 sequence alignment computer program, to have certain sequence identity to other known interferon receptors. This cDNA sequence is herein designated DNA48466 (Figure 143; SEQ ID NO:352). Based on the sequence identity, probes were generated from the sequence of the DNA48466 molecule and used to screen a human breast carcinoma

library (LIB135) prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

The oligonucleotide probes employed were as follows:

forward PCR primer 5'-AGGCTTCGCTGCGACTAGACCTC-3' (SEQ ID NO:354)

5 reverse PCR primer 5'-CCAGGTCGGTAAGGATGGTTGAG-3' (SEQ ID NO:355)

hybridization probe

5'-TTTCTACGCATTGATTCCATGTTGCTCACAGATGAAGTGGCCATTCTGC-3' (SEQ ID NO:356)

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 250-252, and a stop signal at nucleotide positions 1183-1185 (Figure 141, SEQ 10 ID NO:351). The predicted polypeptide precursor is 311 amino acids long, has a calculated molecular weight of approximately 35,076 daltons and an estimated pI of approximately 5.04. Analysis of the full-length PRO1114 interferon receptor sequence shown in Figure 142 (SEQ ID NO:352) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 29, a transmembrane domain from about amino acid 230 to about amino acid 255, potential N-glycosylation sites from about amino acid 40 to about amino acid 43 and from 15 about amino acid 134 to about amino acid 137, an amino acid sequence block having homology to tissue factor proteins from about amino acid 92 to about amino acid 119 and an amino acid sequence block having homology to integrin alpha chain proteins from about amino acid 232 to about amino acid 262. Clone UNQ557 (DNA57033-1403) has been deposited with ATCC on May 27, 1998 and is assigned ATCC deposit no. 209905.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment 20 analysis of the full-length sequence shown in Figure 142 (SEQ ID NO:352), evidenced significant homology between the PRO1114 interferon receptor amino acid sequence and the following Dayhoff sequences: G01418, INR1_MOUSE, P_R71035, INGS_HUMAN, A26595_1, A26593_1, I56215 and TF_HUMAN.

EXAMPLE 55: Isolation of cDNA Clones Encoding Human PRO237

25 A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA30905. Based on the DNA30905 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO237.

PCR primers (forward and reverse) were synthesized:

30 forward PCR primer 5'-TCTGCTGAGGTGCAGCTCATTCA-3' (SEQ ID NO:359)

reverse PCR primer 5'-GAGGCTCTGGAAGATCTGAGATGG-3' (SEQ ID NO:360)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA30905 sequence which had the following nucleotide sequence

hybridization probe

35 5'-GCCTCTTGTCACGTTGCCAGTACCTCTAACCCATTCCAGTCGCCTC-3' (SEQ ID NO:361)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO237 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal brain tissue (LIB153).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO237 [herein designated as UNQ211 (DNA34353-1428)] (SEQ ID NO:357) and the derived protein sequence for PRO237.

The entire nucleotide sequence of UNQ211 (DNA34353-1428) is shown in Figure 144 (SEQ ID NO:357). Clone UNQ211 (DNA34353-1428) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 586-588 and ending at the stop codon at nucleotide positions 1570-1572 (Figure 144). The 5 predicted polypeptide precursor is 328 amino acids long (Figure 145). The full-length PRO237 protein shown in Figure 145 has an estimated molecular weight of about 36,238 daltons and a pI of about 9.90. Analysis of the full-length PRO237 sequence shown in Figure 145 (SEQ ID NO:358) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 23, a transmembrane domain from about amino acid 177 to about amino acid 199, potential N-glycosylation sites from about amino acid 118 to about amino acid 121, from about 10 amino acid 170 to about amino acid 173 and from about amino acid 260 to about amino acid 263 and eukaryotic-type carbonic anhydrase sequence homology blocks from about amino acid 222 to about amino acid 270, from about amino acid 128 to about amino acid 164 and from about amino acid 45 to about amino acid 92. Clone UNQ211 (DNA34353-1428) has been deposited with ATCC on May 12, 1998 and is assigned ATCC deposit no. 209855.

Analysis of the amino acid sequence of the full-length PRO237 polypeptide suggests that it possesses 15 significant sequence similarity to the carbonic anhydrase protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO237 amino acid sequence and the following Dayhoff sequences, AF050106_1, OACALP_1, CELD1022_8, CAH2_HUMAN, 1CAC, CAH5_HUMAN, CAHP_HUMAN, CAH3_HUMAN, CAH1_HUMAN and 2CAB.

20 **EXAMPLE 56: Isolation of cDNA Clones Encoding Human PRO541**

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA42259. Based on the DNA42259 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO541.

25 PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GGACAGAATTGGGAGCACACTGG-3' (SEQ ID NO:364)

forward PCR primer 5'-CCAAGAGTATACTGTCTCG-3' (SEQ ID NO:365)

reverse PCR primer 5'-AGCACAGATTTCTCTACAGCCCC-3' (SEQ ID NO:366)

reverse PCR primer 5'-AACCACTCCAGCATGTACTGCTGC-3' (SEQ ID NO:367)

30 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA42259 sequence which had the following nucleotide sequence

hybridization probe

5'-CCATTTCAGGTGTTCTGGCCCTGTATGTACACATTACACAGGGCGTG-3' (SEQ ID NO:368)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened 35 by PCR amplification with one of the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO541 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO541 [herein designated as UNQ342 (DNA45417-1432)] (SEQ ID NO:362) and the derived protein sequence for PRO541.

The entire nucleotide sequence of UNQ342 (DNA45417-1432) is shown in Figure 146 (SEQ ID NO:362). Clone UNQ342 (DNA45417-1432) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 469-471 and ending at the stop codon at nucleotide positions 1969-1971 (Figure 146). The predicted polypeptide precursor is 500 amino acids long (Figure 147). The full-length PRO541 protein shown in Figure 147 has an estimated molecular weight of about 56,888 daltons and a pI of about 8.53. Analysis of the full-length PRO541 sequence shown in Figure 147 (SEQ ID NO:363) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 20, amino acid sequence blocks having homology to extracellular proteins SCP/Tpx-1/Ag5/PR-1/Sc7 from about amino acid 165 to about amino acid 186, from about amino acid 196 to about amino acid 218, from about amino acid 134 to about amino acid 146, from about amino acid 96 to about amino acid 108 and from about amino acid 58 to about amino acid 77 and a potential N-glycosylation site from about amino acid 28 to about amino acid 31. Clone UNQ342 (DNA45417-1432) has been deposited with ATCC on May 27, 1998 and is assigned ATCC deposit no. 209910.

Analysis of the amino acid sequence of the full-length PRO541 polypeptide suggests that it possesses significant sequence similarity to a trypsin inhibitor protein, thereby indicating that PRO541 may be a novel trypsin inhibitor. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO541 amino acid sequence and the following Dayhoff sequences, D45027_1, AB009609_1, JC5308, CRS3_HORSE, TPX1_HUMAN, HELO_HELHO, GEN14351, A28112_1, CET05A10_4 and P_W11485.

EXAMPLE 57: Isolation of cDNA Clones Encoding Human PRO273

A consensus sequence was obtained relative to a variety of EST sequences as described in Example 1 above, wherein the consensus sequence obtained is herein designated DNA36465. Based on the DNA36465 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO273.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CAGCGCCCTCCCCATGTCCCTG-3' (SEQ ID NO:371)

25 reverse PCR primer 5'-TCCCAACTGGTTGGAGTTTCCC-3' (SEQ ID NO:372)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA36465 sequence which had the following nucleotide sequence

hybridization probe

5'-CTCCGGTCAGCATGAGGCTCCTGGCGGCCGCTGCTCCTGCTGCTG-3' (SEQ ID NO:373)

30 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO273 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO273 35 [herein designated as UNQ240 (DNA39523-1192)] (SEQ ID NO:369) and the derived protein sequence for PRO273.

The entire nucleotide sequence of UNQ240 (DNA39523-1192) is shown in Figure 148 (SEQ ID NO:369). Clone UNQ240 (DNA39523-1192) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 167-169 and ending at the stop codon at nucleotide positions 500-502 (Figure 148). The predicted polypeptide precursor is 111 amino acids long (Figure 149). Clone UNQ240 (DNA39523-1192) has been